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An Exploratory Clinical Study on Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure （HERE-CHF）

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Abstract for protocol

Introduction

Patients with Chronic heart failure (CHF) can benefit from exercise rehabilitation (ER) with significant improvements in exercise capacity, quality of life, and reduction in hospitalizations. Despite its reported benefits, only a limited number of patients with CHF attend ER because of poor adherence and improper exercise may even cause adverse events. Remote electrocardiogram monitoring system (REMS) has the potential to overcome these barriers. We hypothesize that home-based cardiac ER using REMS in CHF patients is effective compared with conventional ER without monitoring.

Methods and Analysis

This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness of home-based ER with REMS in the management of CHF, which has a target enrollment of 120 stable CHF patients (Left Ventricular Ejection Fraction <50%, NYHA classes I to III). Patients are randomized to either REMS rehabilitation group or the conventional rehabilitation group. In the REMS exercise group, patients wearing monitors when exercising to ensure that exercise intensity is within the ranges set for them. REMS will also detect risky arrhythmia and give an early warning to both the patients and their doctors. The training intensity is not monitored in the conventional rehabilitation group. The primary outcome measure is exercise capacity improvement measured by peak oxygen uptake.

Ethics and Dissemination

This study was approved by Ethics Committee of China-Japan Friendship Hospital for Clinical Research （No. 2017-SFZX-9, 10 Aug 2017）, registered on 22 August 2017 at the website of Chinese Clinical Trial Registry (ChiCTR-RNR-17012446) and conducted in accordance with the principles of Good Clinical Practice (GCP) and the Helsinki Declaration. All participants must sign a written informed consent before randomization.

Strengths and limitations of this study

1. Our wearable monitor in this study has been approved by Food and Drug Administration in Shandong province of China (Certificate No. Shandong Medical Device Registration Approval 20172210878).
2. Our REMS will help to increase CHF patients' adherence and reduce risk factors when exercising, which may further enhance the effectiveness of ER.
3. The **HERE-CHF** study will provide new insights in the effect of home-based cardiac ER guided by REMS.
4. The major limitation of this single-center study is the small sample size.
5. A long-term follow-up may be also needed. Extending the exercise out to 6 months may give us better data on adherence.

Keywords: Cardiac exercise rehabilitation, Telerehabilitation, Chronic heart failure, Remote Electrocardiogram Monitoring System

Background

Heart failure (HF) is a complex clinical syndrome caused by abnormal cardiac structure or function which results in impaired ventricular filling or ejection ability. It is the terminal stage of various cardiovascular diseases, which has become the global public health problem of great concern. The prevalence of HF in the whole population is approximately 1.5%-2% and 6%-10% over 65 years of age [1]. More and more individuals are surviving an acute cardiovascular attack due to modern therapies now and the concomitant burden of chronic HF (CHF) is also increasing worldwide. At present, there are 8-10 million patients with HF in China, and the prevalence rate increases significantly with age according to China Cardiovascular report 2017[2]. The 5-year survival rate of HF patients with clinical symptoms is 50% , similar to that of malignant tumors[1]. Repeated visits and hospitalizations of HF patients bring heavy economic burdens to individuals, families and society.

Many HF patients on optimal cardiovascular drug therapy still suffer from dyspnea and exercise intolerance. In addition to pharmacological treatment and device therapy, successful cardiac rehabilitation is a valuable intervention for improving aerobic fitness and overall health status in patients with HF. There is a growing consensus that exercise has a beneficial effect on patients with cardiovascular disease, even for those with severely impaired cardiac function. HF patients can benefit from proper exercise with significant improvements in exercise capacity, quality of life, and reduction in hospitalizations. Exercise training is a core component of primary and secondary prevention, which has been recommended by relevant international professional associations[3-6].

Despite its reported benefits, a limited number of patients attend exercise rehabilitation (ER) on a regular basis mainly because of poor patients' adherence. Furthermore, improper exercise may even cause adverse cardiovascular events such as myocardial infarction, tachyarrhythmias and sudden death. HF-A Controlled Trial Investigating Outcomes of exercise training (HF-ACTION)[7] is the largest multicenter clinical study of ER in HF, which randomly assigned 2331 patients to

either exercise training or usual care. Only Forty-two percent of subjects in their cohort completed all three of their scheduled follow-up exercise tests and 33% and 25% completed two and one of their scheduled follow-up exercise tests, respectively. Given the observed effect between higher adherence and improved outcomes, it is more important to provide cardiac ER programs which can achieve increased adherence to the exercise intervention [8].

Cardiac telerehabilitation using monitoring devices and remote communication with patients has now been used more and more in the long-term management of cardiovascular diseases outside the hospital environment. Providing objective feedback data and allowing patients to track their own progress can increase patients' self-management skills and thus improve their adherence. It is convenient and can reduce anxiety; improve the quality of life, compliance and prognosis of patients with low medical costs compared with conventional ER [9-13].

This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness and safety of home-based ER under the guidance of remote electrocardiogram （ECG）monitoring system（REMS） in the management of CHF. This article describes the design and rationale of the **HERE-CHF** trial supported by China Capital Health Development Research Special Fund of 2018.

Methods/design

Aims

The primary objective of **HERE-CHF** trial is to test the hypothesis that individualized home-based cardiac ER using REMS to guide patients with LV systolic dysfunction【LVEF<50%, New York Heart Association（NYHA）classification I-III）】 is effective and safe with the advantages of standardization and easy implementation compared with conventional ER without monitoring. The primary outcome measure is exercise tolerance measured by peak oxygen uptake (VO_2) at baseline and three months. Secondary outcome measures include 6-min Walk Test (6MWT), NYHA classifications, echocardiographic parameters, cardiac biomarkers, major adverse cardiovascular events (MACE), quality of life, psychological state and patients'

compliance.

Design

A flow chart of the study design is shown in Figure 1. The study strategy is registered on the website of Chinese Clinical Trial Registry (ChiCTR-RNR-17012446, registered on 22 August 2017), constructed and presented according to the recommendations for Interventional Trials (SPIRIT) [14].

Study sites and Patient population

Patients are recruited consecutively from the Cardiology Department of China-Japan Friendship Hospital in Beijing, China. Patient selection criteria are listed in Table 1. CHF had to be documented from at least one echocardiogram performed within the previous 6 weeks under clinically stable conditions.

HERE-CHF trial has a target enrollment of 120 stable CHF patients （LVEF<50%, NYHA classes I to III） based on a predefined set of inclusion and exclusion criteria (Table I). Patients must have an LV ejection fraction (LVEF) of <50% on a baseline echocardiogram. Stable optimal pharmacologic therapy according to the published guidelines for 6 weeks before enrollment is strongly advocated. If patients are not treated with optimal HF pharmacologic treatment as defined by the American College of Cardiology(ACC)/American Heart Association (AHA) HF guidelines (ie, angiotensin-converting enzyme inhibitors and β-blockers), then trial personnel must document the underlying reason (eg, drug intolerance).

Exercise testing

Prerandomization cardiopulmonary exercise testing (CPET) is used to determine whether patients can exercise safely as defined by the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines, including checking for abnormal blood pressure responses, early ischemic changes, and significant arrhythmias. Exercise testing is repeated 3 month after randomization for all patients. The primary method used for exercise testing is cycling, consistent with AHA guidelines and with other trials that have assessed exercise capacity in patients with HF.

Randomization

After providing informed consent and undergoing baseline testing (echocardiogram and CPET), patients are randomized at the enrolling center in a 1:1 ratio to either REMS rehabilitation arm or the conventional rehabilitation arm.

Trial structure

The trial structure of the study is described in the Table 2.

REMS

Inticare-MC-06 wearable ECG monitor (Elephant Medical Electronic Technology, Jining, China), which is approved by Food and Drug Administration in Shandong province of China（Certificate No. Shandong Medical Device Registration Approval 20172210878）is a medical-grade portable cardiac monitor which looks like a smaller “Band-Aid” and can collect single-lead ECG data for 48 hours. It can provide cardiac care service through "Hardware+Software+ Cloud + Doctor" program, and support arrhythmia automatic trigger and One-Tap SOS. Its goal is to reduce health care cost, detect arrhythmia earlier, get treatment timely and provide better service for heart health. Inticare-MC-06 heart health monitor solution includes 5 parts: inticare-M1 wearable ECG monitor, mobile terminals (such as smart phones), cloud data storage platform （Tianjin AILife Medical Technology, China）, cardiologists and monitoring reports. Wearable ECG monitor will be pasted on the chest through one-piece electrodes and transfer the ECG data to the mobile phone application via lower power bluetooth smart technology. The unique algorithm can analyze the data in real time and detect suspected arrhythmia disease, then give the alarm and transfer data to cloud for doctors to check and confirm the disease. In addition, when you feel chest stuffy, heart palpitations and dizzy, you can mark the ECG data during this 1 minute through One-Tap Marking button and send the data to cloud for doctors to check and give corresponding diagnosis. At the end of the monitoring, inticare-M1 can provide the monitoring report.

Interventions

All the patients initiate an exercise training program following the principles of

exercise prescription as recommended by the American College of Sports Medicine (ACSM) and the AHA. The exercise stage order can be warm-up, main exercise, and cool-down. For the warm-up and cool-down, walking or light stretching is recommended. The main exercise is walking. Exercise training initially begins in a supervised setting and then transitions to a home-based regimen(Table 3 and table 4). The supervised training phase of the trial consists of 12 supervised training sessions, with a goal of 3 sessions per week. Patients have up to 1 month to complete the 12 sessions before transitioning to the home exercise phase of the trial. Patients are asked to exercise 5 times per week during the home exercise phase, totally 8 weeks. The exercise training protocol was designed such that patients begin exercising at a low intensity and then increase to a moderate intensity when they are able. The trial protocol allows patients to walk independently.

In the REMS exercise training arm, patients wear Inticare-MC-06 ECG monitor when exercising at home to ensure that exercise intensity is within the ranges set for them and are instructed on how to monitor their own exercise training at the beginning of the trial. During the exercise, the monitor can evaluate whether patients reach the intensity and time of the preset exercise prescription according to the heart rate. If the speed is not enough or the intensity exceeds the preset value, the system uses voice prompt to remind the patient to adjust the intensity, including speed and time course, so as to ensure the patient to exercise according to the prescription. If a cardiogram such as arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. The data will be transformed to the data center, while specialist will give an analysis for that report. System will give an early warning to both the user and their doctors if the arrhythmia event they get is risky. Doctors can have a check of the data belong to their patient outside hospitals, know about their condition and give advice in time.

The heart rate reserve (HRR) method is used to guide exercise intensity. Peak heart rate is derived from a patient's most recent exercise test, and the resting heart rate is taken after 5 minutes of quiet seated rest. For the first 6 supervised training sessions,

the training heart rate range is computed at 60% of the HRR (resting heart rate + 0.6 [peak heart rate resting heart rate]). Then training intensity is increased to 70% of the HRR for the rest of the supervised exercise training sessions. For the home-based exercise training phase, patients are asked to perform 40 minutes of aerobic exercise. In the REMS training arm, the training intensity should be maintained at 60% to 70% of the HRR. While during the whole phase of the conventional rehabilitation arm, the training intensity is not monitored.

Outcome assessments

The primary outcome measure is exercise capacity improvement measured by VO_2 (baseline vs 3 m). The secondary outcome measures are: (1) difference in the meters walked in the 6MWT; (2) improvement in heart function assessed by NYHA classifications; (3) improvement in echocardiographic parameters of systolic and diastolic function; (4)changes in biomarkers, including brain natriuretic peptide (BNP) / N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) and Troponin-T/I; (5) changes in major adverse cardiovascular events (MACE) including worsening HF event, HF hospitalization, myocardial infarction, stroke, revascularization and cardiovascular mortality; (6) qualitative evaluation of patients' compliance to the rehabilitation program. The investigators will also use several validated psychometric instruments to measure health-related quality of life and depression. These measurements include HF Symptom Scale , Minnesota Living with Heart Failure Questionnaire (MLHFQ), 36-Item Short Form Health Survey (SF-36), Beck Depression Inventory-II (BDI-II) and General Self-Efficacy Scale (GSE).

Withdrawal

According to Ethics Committee of China-Japan Friendship Hospital for Clinical Research legislations, we inform the patients about their rights as subjects in a scientific trial and about their discontinuation rights. We do this to make patients consider participation thoroughly to diminish the likelihood of their dropping out. Patients can withdraw from the trial at their own request or at the request of their legal representative at any time. Every withdrawal was recorded in the patient's health

record.

Data collection, management, and analysis

We collect and manage study data using HF Rehabilitation-CARELAND database (Beijing Cardiar Technology, China). Only relevant staff have logged access to the key file. The principal investigator has a responsibility to secure and monitor data collection and interpretation.

Adverse events monitoring

All adverse events that occurred during the 3-month study observation period will be reported in the final paper. A serious adverse event is defined as any untoward medical occurrence resulting in hospitalization or which results in a life-threatening problem, death, or disability. Adverse events will be defined as any untoward occurrences in study participants, potentially related to implementation of the study protocol. All serious and unexpected adverse events will be reported to the Ethics Committee as required.

Sample size

The target enrollment for the trial is 120 patients. A total of 500 patients with CHF (NYHA grade I-III) are treated in our hospital every year , which can be used as a screening sample. Calculated according to the lower screening rate (50%) and the designed entry criteria, the sample size that can be completed is estimated to be100 patients. Referring to the previous foreign literature, the compliance of ER in 3 months is 70-80%. The initial screening sample size of this study is at least 120 cases, 60 cases in each group.

Statistical analysis

The clinical data management platform of China-Japan Friendship Hospital is commissioned to create SAS 9.4 software to generate random concealment tables. Masked envelopes will be produced by random concealment and participants are admitted by 1:1 random principle. After screening for the inclusion and exclusion criteria, the patients are randomly enrolled in the REMS rehabilitation group or the conventional rehabilitation group according to the time order of the patients' entry.

The number of each subject remains unchanged during the course of the study. All statistical tests will be 2-tailed. All data are presented as the mean±the standard deviation (SD). Comparison of numerical variables between the study groups is made using Student's t-test for independent samples in comparing 2 groups when normally distributed and Mann–Whitney U-test for independent samples when not normally distributed. $P<0.05$ is considered significant.

Patient and Public Involvement

Enrollment of patients has started in April 2018. Patients are recruited consecutively from the outpatient clinic of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by the doctors in the study.

Discussion

HERE-CHF evaluates the effect of a cardiac telerehabilitation intervention that combines modern technology (sensor technology, internet and remote consultation) with evidence-based ER guidance strategies including prevention of adverse events when exercising. The objective of this study is to investigate whether home-based cardiac ER using REMS is superior to conventional ER without monitoring in CHF patients. We hypothesize that this intervention will result in improved physical activity levels and better quality of life.

Home-based cardiac rehabilitation is a method to improve participation rate of ER in HF patients. Whether exercise prescription can be efficiently performed and the safety in exercise are two main issues in home-based ER. While exercise intensity is the key of exercise prescription because the exercise has to be appropriate. Heart rate is the most important factor to monitor the patient's exercise intensity. Our wearable ECG monitor can evaluate whether patients reach the intensity according to the heart rate and remind the patients in time so as to ensure that exercise intensity is within the preset range. REMS will also detect risky arrhythmia and give an early warning to both the patients and their doctors, which can encourage patients to overcome fear and adhere to exercise. The use of our REMS offers a prospect for the delivery and expansion of home-based cardiac ER programs in HF patients beyond the supervised

setting and will help to increase adherence, reduce risk factors and improve benefit-cost ratio，which may further enhance the effectiveness of ER.

CPET is useful to evaluate patient exercise capacity and exertional symptoms and can offer numerous physiologic parameters. Multiple CPET-derived variables have been assessed for their association with mortality in systolic HF patients and peak VO_2 is shown to be the strongest predictor of mortality [15]. Therefore we select it as the primary outcome measure in CR-HERES-CHF. The choice of the 6MWT as a secondary outcome measure due to its useful prognostic information similar to peak VO_2[16]. 6MWT is less expensive and much more convenient in comparison to the nontrivial costs of CPET with its distinctive value as a measure of routine activity. Quality of life and psychological state are important in the evaluation of home-based ER, which are also included in our study.

Conclusion

The **HERE-CHF** study will provide new insights in the effect of home-based cardiac ER guided by REMS. Our REMS will help to increase HF patients' adherence and reduce risk factors, which may further enhance the effectiveness of ER.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by Ethics Committee of China-Japan Friendship Hospital for

Clinical Research （No. 2017-SFZX-9, 10 Aug 2017）, registered on 22 August 2017 at the website of Chinese Clinical Trial Registry (ChiCTR-RNR-17012446) and conducted in accordance with the principles of Good Clinical Practice (GCP) and the Helsinki Declaration. All participants must sign a written informed consent before randomization.

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Table 1. HERES-CHF trial inclusion and exclusion criteria

Inclusion criteria
1. Aged 18-75 years old;
2. chronic heart failure (NYHA I-III); LVEF<50% in 6 weeks before randomization;
3. in stable condition after heart failure standard drug therapy (do not need intravenous diuretics, vasoconstrictors, vasodilators or left ventricular assist device), no fluid retention, constant weight;
4. able to perform exercise rehabilitation;
5. clearly understand the content and purpose of the study and volunteer to participate in the study and sign the informed consent form.
Exclusion criteria
1. exercise rehabilitation can not be carried out due to physical disability and contraindication;
2. with a contraindication to cardiopulmonary exercise test;
3. the following was happened in 3 months before admission: acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid artery or other major vascular surgery; percutaneous coronary intervention (PCI)or carotid artery angioplasty; sustained ventricular tachycardia or fibrillation;
4. coronary revascularization or heart transplantation is planned;
5. persistent atrial arrhythmias ; ventricular arrhythmias were not effectively controlled (using an antiarrhythmic drug or an implantable defibrillator);
6. uncorrected primary obstructive or severe regurgitant heart valve disease, restrictive or hypertrophic cardiomyopathy;
7. II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for heart failure;
8. obstructive or bronchospasm lung disease(such as asthma, bronchitis, etc) needing oral or inhaled bronchodilator or glucocorticoids therapy;
9. pregnant or lactating women and those planning to conceive during the trial;

10. cancer or other systemic diseases with an expected survival of less than 12 months; 11. other clinical trial drugs were taken or in other medical device trial within 30 days before admission; 12. unable to participate in this study after the clinical evaluation by investigators.

Table 2 Trial structure of the study

Time / Assessment	Screening (-14~-1d)	Exercise Rehabilitation in Clinic			Exercise Rehabilitation at Home	
		T0 Visit 1 Baseline	T1 Visit 2 2nd weekend	T2 Visit 3 4th weekend	T3 Visit 4 8th weekend	T4 Visit 5 12th weekend
medical history	√					
Inclusion/Exclusion Form	√					
Consent Form	√					
Comorbidity	√	√	√	√	√	√
Concomitant medication	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√
Troponin T/I		√				√
BNP/NT-proBNP		√				√
Electrocardiogram	√	√		√	√	√
Holter	√					√
NYHA classification	√	√		√	√	√
Echocardiography	√	√				√
CPET	√					√
6MWT		√				√

Heart failure symptom scale		√				√
MLHFQ		√				√
SF-36		√				√
BDI-II		√				√
GSE		√				√
Compliance				√	√	√
Adverse event			√	√	√	√
Monitor and APP training		√				

The time window for each visit is ±3d. MLHFQ: Minnesota Living with Heart Failure Questionnaire. SF-36: 36-Item Short Form Health Survey. BDI-II: Beck Depression Inventory. GSE: General Self-Efficacy Scale.

Table 3. Exercise training program in remote ECG monitoring system rehabilitation group

Training phase	Location	week	Weekly sessions	Aerobic duration (min)	Intensity (percentage of HRR)	Mode of exercise
Initial,supervised by Rehabilitation specialist	Clinic	2	3	15-30	60	walk
supervised by Rehabilitation specialist	Clinic	2	3	15-30	70	walk
Supervised by remote ECG monitoring	home	8	5	40	60-70	walk

Table 4. Exercise training program in conventional rehabilitation group without monitoring

Training phase	Location	week	Weekly sessions	Aerobic duration (min)	Intensity (percentage of HRR)	Mode of exercise
Initial, supervised by Rehabilitation specialist	Clinic	4	3	15-30	without monitoring	walk
Symptom-Limited, self-adaption	home	8	5	40	without monitoring	walk

Legends

Figure 1 Study flow chart. CPET: cardiopulmonary exercise testing. 6MWT:6-min Walk Test.

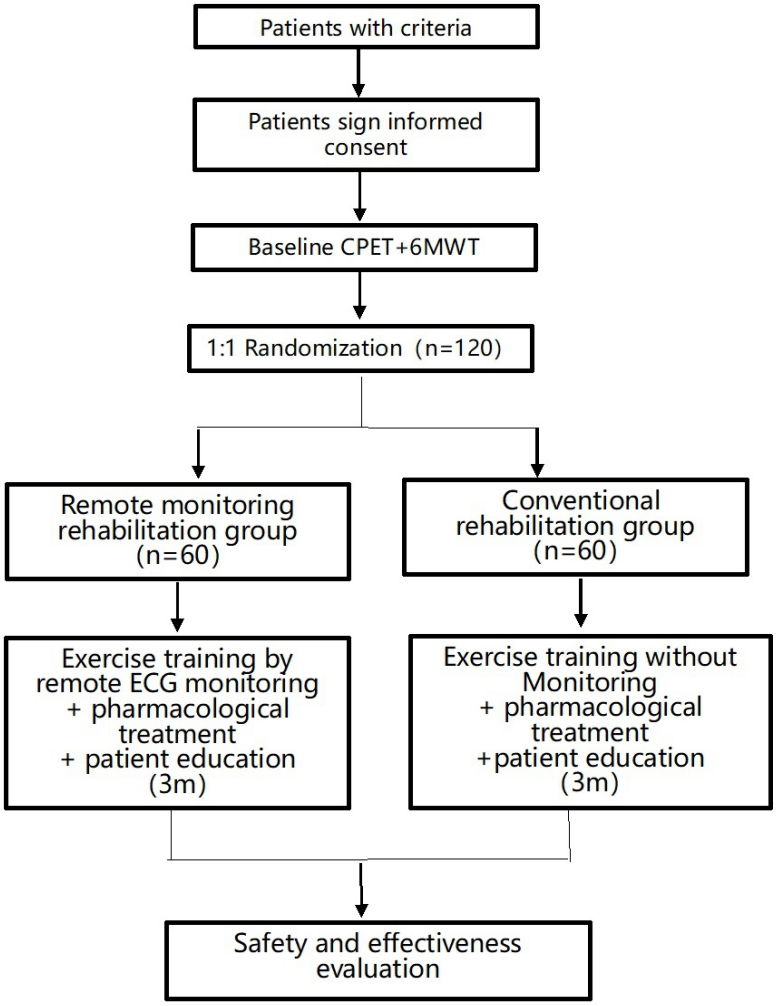

Figure 1 Study flow chart.

170x233mm (144 x 144 DPI)

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Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure（HERE-CHF）：Study Protocol for a Randomized Controlled Trial

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Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure (HERE-CHF): Study Protocol for a Randomized Controlled Trial

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Abstract

Introduction

Patients with chronic heart failure (CHF) can benefit from exercise rehabilitation (ER) with significant improvements in exercise capacity, quality of life, and reduction in hospitalizations. Despite its reported benefits, only a limited number of patients with CHF attend ER because of pooer adherence and improper exercise may even cause adverse events. Remote electrocardiogram monitoring system (REMS) has the potential to overcome these barriers. We hypothesize that home-based cardiac ER using REMS in CHF patients is effective compared with conventional ER without monitoring.

Methods and Analysis

This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness of home-based phase-II ER with REMS in the management of CHF, which has a target enrollment of 120 patients 【Left Ventricular Ejection Fraction <50%, New York Heart Association (NYHA) classes I to III】. Patients are randomized to either REMS rehabilitation group or conventional rehabilitation group in a 1:1 ratio. All the patients initiate an exercise training in a supervised setting and then transition to a home-based regimen. The supervised training phase consists of 12 supervised training sessions, 3 sessions per week for 4weeks. During the home exercise phase, patients exercise 5 times per week, totally 8 weeks. In REMS group, patients wear monitors during exercise to ensure that exercise intensity is within the ranges set for them. REMS will also detect risky arrhythmia and give an early warning to both the patients and their doctors. The training intensity is not monitored in the conventional rehabilitation group. The primary outcome is exercise capacity improvement measured by peak oxygen uptake (VO_2 peak) (baseline vs 3 m). Secondary outcomes include 6-min Walk Test (6MWT), NYHA classes, echocardiographic parameters, cardiac biomarkers, major adverse cardiovascular events (MACE), quality of life, psychological well-being and patients' adherence to

the rehabilitation program.

Ethics and Dissemination

This study was approved by Ethics Committee of China-Japan Friendship Hospital for Clinical Research（No. 2018-55-K39）. The results of this study will be disseminated via peer-reviewed publications and presentations at conferences.

Clinical trial registration number

ChiCTR-RNR-17012446

Strengths and limitations of this study

1. The wearable monitor used in this study is a portable cardiac monitor which can collect single-lead electrocardiogram（ECG）data for 48 hours. During the exercise, the monitor can evaluate patients' exercise intensity according to their heart rate and then remind them promptly to exercise appropriately, which may further enhance the effectiveness of ER. This monitor has been approved by Food and Drug Administration in Shandong province of China (Certificate No. Shandong Medical Device Registration Approval 20172210878).
2. The REMS used here can detect arrhythmia and give an early warning to both the exercising patients and their doctors so as to further reduce risks. It allows patients to exercise more safely and patients are also more willing to exercise. The REMS may help improve patients' adherence to ER.
3. Our cardiac ER program is home-based and convenient for CHF patients compared with facility-based ER. This may provide new insights in cardiac telerehabilitation in heart failure patients.
4. The major limitation of this single-center study is the small sample size.
5. A long-term follow-up may be also needed. Extending the exercise out to 6 months may give us better data on adherence.

Keywords: Cardiac exercise rehabilitation, Telerehabilitation, Chronic heart failure, Remote Electrocardiogram Monitoring System

Introduction

Heart failure (HF) is a complex clinical syndrome caused by abnormal cardiac structure or function which results in impaired ventricular filling or ejection ability. It is a terminal stage of various cardiovascular diseases, which has become the global public health problem of great concern. The prevalence of HF in the whole population is approximately 1.5%-2% and 6%-10% over 65 years of age [1]. More and more individuals are surviving an acute cardiovascular attack due to modern therapies now and the concomitant burden of chronic HF (CHF) is also increasing worldwide. At present, there are 8-10 million patients with HF in China, and the prevalence rate increases significantly with age according to China Cardiovascular report 2017[2]. The 5-year survival rate of HF patients with clinical symptoms is 50%，similar to that of malignant tumors[1]. Repeated visits and hospitalizations of HF patients bring heavy economic burdens to individuals, families and society.

Many HF patients on optimal cardiovascular medical therapy still suffer from dyspnea and exercise intolerance. In addition to medical treatment and device therapy, successful cardiac rehabilitation (CR) is a valuable intervention for improving aerobic fitness and overall health status in patients with HF. There is a growing consensus that exercise has a beneficial effect on patients with cardiovascular disease, even for those with severely impaired cardiac function. HF patients can benefit from proper exercise with significant improvements in exercise capacity, quality of life, and reduction in hospitalizations. Exercise training is a core component of primary and secondary prevention, which has been recommended by relevant international professional associations[3-6].

Despite its reported benefits, a limited number of HF patients attend exercise rehabilitation（ER）on a regular basis mainly because of poor patients' adherence. Furthermore, improper exercise without monitoring may even cause adverse

cardiovascular events such as myocardial infarction, arrhythmias and sudden death. HF-A Controlled Trial Investigating Outcomes of exercise training (HF-ACTION)[7] is the largest multicenter clinical study of ER in HF, which randomly assigned 2331 patients to either exercise training or usual care. Only Forty-two percent of subjects in their cohort completed all three of their scheduled follow-up exercise tests and 33% and 25% completed two and one of their scheduled follow-up exercise tests, respectively. Given the observed effect between higher adherence and improved outcomes, it is more important to provide cardiac ER programs which can achieve increased adherence to the exercise intervention [8].

Cardiac telerehabilitation using monitoring devices and remote communication with patients has now been used more and more in the long-term management of cardiovascular diseases outside the hospital environment. Providing objective feedback data and allowing patients to track their own progress can increase patients' self-management skills and thus improve their adherence. It is convenient and can reduce anxiety, improve the quality of life and prognosis of patients with low medical costs compared with conventional ER without monitoring [9-13].

This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness and safety of home-based phase-II ER under the guidance of remote electrocardiogram (ECG) monitoring system (REMS) in the management of CHF compared with conventional ER without monitoring. This article describes the design and rationale of the **HERE-CHF** trial.

Methods/design

Design

A flow chart of the study design is shown in Figure 1. The protocol is constructed and presented according to the recommendations for Interventional Trials (SPIRIT) [14]. The study protocol (V1.1, 20180208) and informed consent documents (V1.1, 20180208) have been reviewed and approved by the Ethics Committee of China-Japan Friendship Hospital for Clinical Research. If there is any amendment to the protocol, approval must be sought again from the Ethics Committee. The study

strategy has been registered on the website of Chinese Clinical Trial Registry (ChiCTR-RNR-17012446, registered on 22 August 2017), and the trial will be performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Eligibility and recruitment

Patient selection criteria are listed in Table 1. Patients must have a systolic cardiac dysfunction documented from a baseline echocardiogram【LV ejection fraction (LVEF) <50%】within 6 weeks before randomization who are under stable conditions【New York Heart Association (NYHA) classes I to III】. As defined by the American College of Cardiology(ACC)/American Heart Association (AHA) HF guidelines, stable optimal medical therapy including β blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) and aldosterone receptor antagonists for 6 weeks before enrollment is strongly advocated. If patients are not treated with optimal medical therapy, then trial personnel must document the underlying reason (eg, drug intolerance).

Enrollment of patients has started in April 2018. Patients will be recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who will obtain written consent from patients willing to participate in the trial. Screening will continue until the target population is achieved. A recruitment advertisement has also been utilized in our hospital. No financial incentives will be provided to the attending physicians or patients for enrollment.

Sample size

The target enrollment for the trial is 120 patients. A total of 500 patients with HF (NYHA grade I-III) are treated in our hospital every year , which can be used as a screening sample. Calculated according to the lower screening rate (50%) and the designed entry criteria, the sample size that can be completed is estimated to be 100 patients. Referring to the previous foreign literature, the compliance of ER in 3

months is 70-80%. The initial screening sample size of this study is at least 120 cases, 60 cases in each group.

Exercise testing

Prerandomization cardiopulmonary exercise testing (CPET) is used to determine whether patients can exercise safely as defined by the American Association of Cardiovascular and Pulmonary Rehabilitation guidelines, including checking for abnormal blood pressure responses, early ischemic changes, and significant arrhythmias. Exercise testing is repeated 3 month after randomization for all patients. The primary method used for exercise testing is cycling, consistent with AHA guidelines and with other trials that have assessed exercise capacity in patients with HF.

Randomization and binding

China-Japan Friendship Hospital clinical research data management platform is commissioned to generate a random sequence of 120 numbers using SAS 9.4 software. The random sequence will be put into sealed envelopes by staff not involved with the study to avoid selecting bias. After providing informed consent and undergoing baseline testing (echocardiogram and CPET), patients are randomized in a 1:1 ratio to either REMS rehabilitation group or the conventional rehabilitation group according to the time order of the patients' entry. Allocation concealment will be ensured and the randomization code will not be released until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. Researchers involved in participants' assessments will be blinded to treatment allocation.

Trial structure

The trial structure of the study is described in the Table 2.

REMS

Inticare-MC-06 wearable ECG monitor (Elephant Medical Electronic Technology Co., Ltd, Jining, China), which is approved by Food and Drug Administration in Shandong province of China（Certificate No. Shandong Medical Device Registration Approval

20172210878）is a medical-grade portable cardiac monitor which looks like a smaller "Band-Aid" and can collect single-lead ECG data for 48 hours. It can provide cardiac care service through a "Hardware + Software+ Cloud + Doctor" program, and support arrhythmia automatic trigger and One-Tap SOS. Inticare-MC-06 heart health monitor solution includes 5 parts: a wearable ECG monitor, mobile terminals (such as smart phones), Cardiac Healthcare Cloud Service platform of Elephant Medical（Tianjin AI-Life Medical Technology Co.，Ltd, China）, cardiologists and monitoring reports, which is technically supported by Tianjin Institute of Internet of Things Technology. The wearable ECG monitor is pasted on the chest through one-piece electrodes and transfers the ECG data to the smart phone application of cloud service platform (Elephant Heart Health) via bluetooth smart technology. If a cardiogram such as arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. The data will be transformed to the data center, while specialist will give an analysis for that report. The unique algorithm can analyze the data in real time and detect suspected arrhythmias, then give the alarm and transfer data to cloud platform for doctors to check and confirm the disease. In addition, when patients have chest discomfort, palpitation and dizziness, they can mark the ECG data through One-Tap Marking button and send the data for doctors to check and give corresponding diagnosis. At the end of the monitoring, a report will be provided.

Interventions

All the patients initiate an exercise training program following the principles of exercise prescription as recommended by the American College of Sports Medicine (ACSM) and the AHA. The exercise stage order can be warm-up, main exercise, and cool-down. For the warm-up and cool-down, walking or light stretching is recommended. The main exercise is walking. Exercise training initially begins in a supervised setting and then transitions to a home-based regimen（Table 3 and Table 4）. The supervised training phase consists of 12 supervised training sessions, with a goal

of 3 sessions per week. Patients have up to 1 month to complete the 12 sessions before transition to the home exercise phase. Patients are asked to exercise 5 times per week during the home exercise phase, totally 8 weeks. Patients begin exercising at a low intensity and then increase to a moderate intensity when they are able. The trial protocol allows patients to walk independently.

In the REMS group, patients wear Inticare-MC-06 ECG monitors when exercising at home to ensure that exercise intensity is within the ranges set for them and are instructed on how to monitor their own exercise training at the beginning of the trial. During the exercise, the monitor can evaluate whether patients reach the intensity and time of the preset exercise prescription according to the heart rate. If the speed is not enough or the intensity exceeds the preset value, the system can remind the patient promptly to adjust the intensity, including speed and time course, so as to ensure the patient to exercise according to the prescription. If arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. Specialists will give an analysis report. The system will give an early warning to both patients and their doctors if the arrhythmia is risky. Doctors can check the data of their patients outside hospital, know about their conditions and give advice in time.

The heart rate reserve (HRR) method is used to guide exercise intensity. Peak heart rate is derived from a patient's most recent exercise test, and the resting heart rate is taken after 5 minutes of quiet seated rest. For the first 6 supervised training sessions, the training heart rate range is computed at 60% of the HRR (resting heart rate + 0.6 [peak heart rate-resting heart rate]). Then training intensity is increased to 70% of the HRR for the rest of the supervised exercise training sessions. For the home-based exercise training phase, patients are asked to perform 40 minutes of aerobic exercise. In the REMS training arm, the training intensity should be maintained at 60% to 70% of the HRR. While during the whole phase of the conventional rehabilitation arm, the training intensity is not monitored.

Concomitant treatment

Participants in both groups will continue standard therapy for HF. The medication

should remain unchanged during the trial, while the dosage should be adjusted in case of adverse events. All procedures will be determined by physicians following the clinical guidelines.

Adherence

During the training phase, participants will be asked to exercise strictly according to the prescription and record each exercise process with designed cards. Investigators will make telephone reminders before each visit and then give face-to-face reminders at each study visit emphasizing the importance of adherence. Compliance of ER in subjects are expressed in rate.

Outcome assessments

The primary outcome is exercise capacity improvement measured by peak oxygen uptake (VO_2 peak) (baseline vs 3 m). The secondary outcomes are: (1) difference in the meters walked in the 6-min Walk Test (6MWT); (2) improvement in heart function assessed by NYHA classifications; (3) improvement in echocardiographic parameters of systolic and diastolic function; (4)changes in biomarkers, including brain natriuretic peptide (BNP) / N-terminal-pro-brain natriuretic peptide (NT-pro-BNP)and Troponin-T/I; (5) changes in major adverse cardiovascular events (MACE) including worsening HF event, HF hospitalization, myocardial infarction, stroke, revascularization and cardiovascular mortality; (6) qualitative evaluation of patients' adherence to the rehabilitation program. The investigators will also use several validated psychometric instruments to measure health-related quality of life and depression. These measurements include HF Symptom Scale , Minnesota Living with Heart Failure Questionnaire (MLHFQ), 36-Item Short Form Health Survey (SF-36), Beck Depression Inventory-II (BDI-II) and General Self-Efficacy Scale (GSE). Researchers involved in participants' assessments will be blinded to treatment allocation.

Withdrawal

According to Ethics Committee of China-Japan Friendship Hospital for Clinical Research legislations, we inform the patients about their rights as subjects in a

scientific trial and about their discontinuation rights. We do this to make patients consider participation thoroughly to diminish the likelihood of their dropping out. Patients can withdraw from the trial at their own request or at the request of their legal representative at any time.

Data collection, management, and analysis

All patients' data will be recorded by trained clinical researchers using a standardized case report form (CRF). Original data should be recorded timely and accurately. Laboratory reports copies should also be kept. All CRFs will be stored in locked file cabinets in areas with limited access. All laboratory specimens will be identified by a coded number to maintain participant confidentiality. Data managers from Beijing Cardiar Technology, China are responsible for the data entry and management. The database is established by PHP language under Linux system. Two data managers perform double entry independently and proofread to ensure the data accuracy. China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organizers. All individuals involved in data management and analysis will be blinded to treatment allocation. Principal investigators will have direct access to data sets. Data dispersed to project team members will be blinded of any identifying participant information.

Adverse events monitoring

All adverse events that occurred during the 3-month study period will be reported in the final paper. A serious adverse event is defined as any untoward medical occurrence resulting in hospitalization or which results in a life-threatening problem, death, or disability. Adverse events will be defined as any untoward occurrences in study participants, potentially related to implementation of the study protocol. All serious and unexpected adverse events will be reported to the Ethics Committee as required.

Statistical analysis

Continuous variables will be presented as the mean ±standard deviation (SD), median or interquartile range (IQR). Baseline characteristics of the cohort will be summarized using descriptive statistics. Whether imbalances exist will be analyzed between

groups. Comparison of numerical variables between the two groups is made using Student's t-test for independent samples when normally distributed. Categorical variables will be described as frequencies and percentages and compared using $\chi 2$ test. Mann-Whitney U test will be used if data are not normally distributed.

Analysis of outcomes will be conducted according to the intention-to-treat (ITT) principle. We will use three analysis sets: full analysis set(FAS), per protocol set(PPS) and safety set. The FAS includes all patients randomized, and the PPS consists of all patients who complete the treatment protocol. The safety set consists of patients who receive at least one treatment with safety records after randomization. Dropouts will be included in the analysis by modern imputation methods for missing data.

All statistical tests will be 2-tailed. $P<0.05$ is considered statistically significant. All statistical analyses will be completed by Beijing Zhengyuan Technology Co., Ltd using SAS 9.4 software.

Patient and Public Involvement (PPI)

During the study design, CHF patients and their relatives were invited to participate in surveys and discussions, which allowed us to know their strong desire in ER, especially home-based telerehabilitation. We also selected several patients to use the monitor, which helped us to identify the problems in application. Besides, we invited medical specialists including cardiologists, rehabilitation therapists and statistical analysts to discuss the study design and revise the intervention method and outcome measures. The results of our study will be disseminated to PPI representatives and study participants who wish to be notified.

Discussion

HERE-CHF evaluates the effect of a cardiac telerehabilitation intervention that combines modern technology (sensor technology, internet and remote consultation) with evidence-based ER guidance strategies including prevention of adverse events when exercising. The objective of this study is to investigate whether home-based cardiac ER using REMS is superior to conventional ER without monitoring in CHF patients. We hypothesize that this intervention will result in improved physical

activity levels and better quality of life.

Home-based CR is a method to improve participation rate of ER in HF patients. Whether exercise prescription can be efficiently performed and the safety in exercise are two main issues in home-based ER. While exercise intensity is the key of exercise prescription because the exercise has to be appropriate. Heart rate is the most important factor to monitor the patient's exercise intensity. Our wearable ECG monitor can evaluate whether patients reach the intensity according to the heart rate and remind the patients in time so as to ensure that exercise intensity is within the preset range. REMS will also detect risky arrhythmia and give an early warning to both the patients and their doctors, which can encourage patients to overcome fear and adhere to exercise. The use of our REMS offers a prospect for the delivery and expansion of home-based cardiac ER programs in HF patients beyond the supervised setting and will help to increase adherence, reduce risk factors and improve benefit-cost ratio，which may further enhance the effectiveness of ER.

CPET is useful to evaluate patient exercise capacity and exertional symptoms and can offer numerous physiologic parameters. Multiple CPET-derived variables have been assessed for their association with mortality in systolic HF patients and peak VO_2 is shown to be the strongest predictor of mortality [15]. Therefore we select it as the primary outcome in **HERE-CHF**. The choice of the 6MWT as a secondary outcome is due to its useful prognostic information similar to peak VO_2[16]. 6MWT is less expensive and much more convenient in comparison to the nontrivial costs of CPET with its distinctive value as a measure of routine activity. Quality of life and psychological state are important in the evaluation of home-based ER, which are also included in our study.

Conclusion

The **HERE-CHF** study will provide new insights in the effect of home-based cardiac ER guided by REMS. Our REMS will help to increase HF patients' adherence and reduce risk factors, which may further enhance the effectiveness of ER.

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Contributors

Xianlun Li, Hong Jiang, Jiahui Li and Peng Yang conceived the original concept of the study, registered the trial and wrote the draft of the protocol manuscript. Dongliang Fu, Xiaojun Ye, Lifang Zhang, Gang Chen, Yiyun Yang, He Luo, Li Chen，Mingjing Shao，Chunyan Li, Yi Liu and Ying Zhou contributed to the design of the study. All the authors read and discussed the manuscript, and approved the final version.

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Competing interests

The authors declare that they have no competing interests.

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Table 1. HERE-CHF trial inclusion and exclusion criteria

Inclusion criteria
1. Aged 18-75 years old; 2. NYHA I-III; LVEF<50% in 6 weeks before randomization; 3. in stable condition after heart failure standard drug therapy (do not need intravenous diuretics, vasoconstrictors, vasodilators or left ventricular assist device), no fluid retention, constant weight; 4. able to perform exercise rehabilitation; 5. clearly understand the content and purpose of the study and volunteer to participate in the study and sign the informed consent form.
Exclusion criteria
1. exercise rehabilitation can not be carried out due to physical disability and contraindication; 2. with a contraindication to cardiopulmonary exercise test; 3. the following was happened in 3 months before admission: acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid artery or other major vascular surgery; percutaneous coronary intervention (PCI)or carotid artery angioplasty; sustained ventricular tachycardia or fibrillation; 4. coronary revascularization or heart transplantation is planned; 5. persistent atrial arrhythmias ; ventricular arrhythmias were not effectively controlled (using

an antiarrhythmic drug or an implantable defibrillator);

6. uncorrected primary obstructive or severe regurgitant heart valve disease, restrictive or hypertrophic cardiomyopathy;

7. II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for heart failure;

8. obstructive or bronchospasm lung disease(such as asthma, bronchitis, etc) needing oral or inhaled bronchodilator or glucocorticoids therapy;

9. pregnant or lactating women and those planning to conceive during the trial;

10. cancer or other systemic diseases with an expected survival of less than 12 months;

11. other clinical trial drugs were taken or in other medical device trial within 30 days before admission;

12. unable to participate in this study after the clinical evaluation by investigators.

Table 2 Trial structure of the study

Time / Assessment	Screening (-14~-1d)	Exercise Rehabilitation in Clinic			Exercise Rehabilitation at Home	
		T0 Visit 1 Baseline	T1 Visit 2 2nd weekend	T2 Visit 3 4th weekend	T3 Visit 4 8th weekend	T4 Visit 5 12th weekend
medical history	√					
Inclusion/Exclusion Form	√					
Consent Form	√					
Comorbidity	√	√	√	√	√	√
Concomitant medication	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√
Troponin T/I		√				√
BNP/NT-proBNP		√				√
Electrocardiogram	√	√		√	√	√
Holter	√					√
NYHA classification	√	√		√	√	√
Echocardiography	√	√				√
CPET	√					√
6MWT		√				√
Heart failure symptom scale		√				√

MLHFQ		√				√
SF-36		√				√
BDI-II		√				√
GSE		√				√
Compliance				√	√	√
Adverse event			√	√	√	√
Monitor and APP training		√				

The time window for each visit is ±3d. MLHFQ: Minnesota Living with Heart Failure Questionnaire. SF-36: 36-Item Short Form Health Survey. BDI-II: Beck Depression Inventory. GSE: General Self-Efficacy Scale.

Table 3. Exercise training program in remote ECG monitoring system rehabilitation group

Training phase	Location	week	Weekly sessions	Aerobic duration (min)	Intensity (percentage of HRR)	Mode of exercise
Initial,supervised by Rehabilitation specialist	Clinic	2	3	15-30	60	walk
supervised by Rehabilitation specialist	Clinic	2	3	15-30	70	walk
Supervised by remote ECG monitoring	home	8	5	40	60-70	walk

Table 4. Exercise training program in conventional rehabilitation group without monitoring

Training phase	Location	week	Weekly sessions	Aerobic duration (min)	Intensity (percentage of HRR)	Mode of exercise
Initial, supervised by Rehabilitation specialist	Clinic	4	3	15-30	without monitoring	walk
Symptom-Limited, self-adaption	home	8	5	40	without monitoring	walk

Legends

Figure 1 Study flow chart. CPET: cardiopulmonary exercise testing. 6MWT: 6-min Walk Test. REMS：remote electrocardiogram monitoring system.

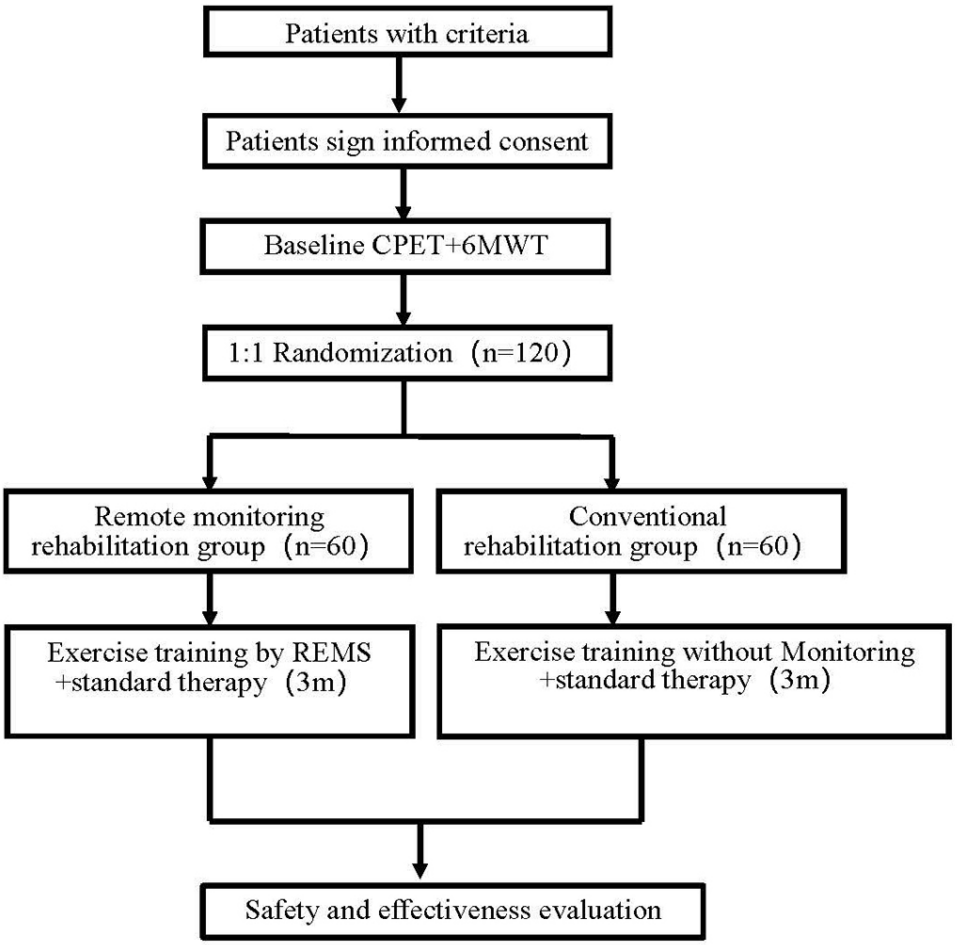

Figure 1 Study flow chart. CPET: cardiopulmonary exercise testing. 6MWT: 6-min Walk Test. REMS : remote electrocardiogram monitoring system.

90x90mm (300 x 300 DPI)

SPIRIT 2013 checklist

Section/item	ItemNo	Information
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym page 1 Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure (HERE-CHF) : Study Protocol for a Randomized Controlled Trial page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page 3 www.chictr.org.cn ChiCTR-RNR-17012446
	2b	All items from the World Health Organization Trial Registration Data Set N/A Registration number： ChiCTR-RNR-17012446 Date of Last Refreshed on： 2017/8/22 10:09:47 Registration Status： 1008001 Prospective registration Public title： An Exploratory Clinical Study on Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart

		Failure			
		Scientific title：	An Exploratory Clinical Study on Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure		
		Applicant：	Li Jiahui	Study leader：	Li Xianlun
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		Applicant address：	2 Yinghua Street East, Chaoyang District, Beijing, China，100029	Study leader's address：	2 Yinghua Street East, Chaoyang District, Beijing, China ,100029
		Applicant's institution：	China-Japan Friendship Hospital		

		Primary sponsor：China-Japan Friendship Hospital Primary sponsor's address：2 Yinghua Street East, Chaoyang District, Beijing, China Source(s) of funding：Self-financing Target disease：heart faliure Study type：Relative factors research Study phase：New Treatment Measure Clinical Study Objectives of Study： To evaluate the efficacy and safety of home-based cardiac exercise rehabilitation with remote electrocardiogram(ECG) monitoring in patients with chronic heart failure(NYHA classification I-III).To demonstrate that home-based exercise rehabilitation with remote ECG monitoring has the advantages of standardization and easy implementation compared with traditional exercise rehabilitation. Study design： Randomized parallel controlled trial Inclusion criteria (1) Aged 18-75 years old, male or female; (2) chronic heart failure (NYHA classification I-III); LVEF<50% in 6 weeks before randomization; (3) in stable condition after heart failure standard

		drug therapy (do not need intravenous diuretics, vasoconstrictors, vasodilators or left ventricular assist device),no fluid retention,constant weight; (4) able to perform exercise rehabilitation; (5) clearly understand the content and purpose of the study and volunteer to participate in the study and sign the informed consent form. Exclusion criteria： 1. exercise rehabilitation can not be carried out due to physical disability and contraindication; 2. with a contraindication to cardiopulmonary exercise test; 3. the following was happened in 3 months before admission: acute coronary syndrome, stroke, transient ischemic attack;cardiac,carotid artery or other major vascular surgery;percutaneous coronary intervention (PCI)or carotid artery angioplasty;sustained ventricular tachycardia or fibrillation; 4. coronary revascularization or heart transplantation is planned; 5. ventricular arrhythmias were not effectively controlled (using an antiarrhythmic drug or an implantable defibrillator); 6. uncorrected primary obstructive or severe regurgitant heart valve disease,restrictive or hypertrophic cardiomyopathy; 7. II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for heart failure; 8. obstructive or bronchospasm lung disease(such as asthma, bronchitis,etc) needing oral or inhaled bronchodilator or glucocorticoids therapy; 9. pregnant or lactating women and those planning to conceive during the trial; 10. cancer or other systemic diseases with an expected survival of less than 12 months; 11. other clinical trial drugs were taken or in other medical device trial within 30 days before admission; 12. unable to participate in this study after the clinical evaluation by

		investigators. Study execute time：From2018/01/01 To 2020/12/31 Interventions： Remote electrocardiogram monitoring group Sample size：60 Control group without monitoring Sample size：60 Countries of recruitment and research settings：China-Japan Friendship Hospital,China Level of the institution：Tertiary A hospital Outcomes：VO2Peak，6 minute walk distance，left ventricular ejection fraction, blood test Randomization Procedure (please state who generates the random number sequence and by what method)： The clinical data management platform of China-Japan Friendship Hospital is commissioned to create SAS 9.4 software to generate random concealment table tables. Masked envelopes will be produced by random concealment and participants are admitted by 1:1 random principle. The time of sharing IPD：Within six months after the trial complete The way of sharing IPD″(include metadata and protocol, If use web-based public database, please

		provide the url)：Publish original data by June 2021 in the form of meetings, speeches or articles.
Protocol version	3	Date and version identifier page 5 20180208 V1.1
Funding	4	Sources and types of financial, material, and other support page 13 This work is financially supported by China Capital Health Development Research Special Fund（2018-2-4064）. Inticare-MC-06 ECG monitors are provided by Tianjin AI-Life Medical Technology Co.，Ltd, China. The funding source does not influence or comment on planned methods, protocol, data analysis, or the draft report.
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors page1, 13 Jiahui Li1*, Peng Yang2*, Dongliang Fu2, Xiaojun Ye1, Lifang Zhang1, Gang Chen3, Yiyun Yang1, He Luo1, Li Chen4，Mingjing Shao2，Chunyan Li2, Yi Liu2，Ying Zhou1, Hong Jiang2※, Xianlun Li1,2※ 1Department of Cardiology, China-Japan Friendship Hospital, Beijing 100029, China; 2Department of Integrative Cardiology, China-Japan Friendship Hospital, Beijing 100029, China; 3Department of Rehabilitation, China-Japan Friendship Hospital, Beijing 100029, China; 4Phase I Clinical Ward of Clinical Trial Research Center, China-Japan Friendship Hospital, Beijing 100029, China.

		※Correspondence: Xianlun Li and Hong Jiang are both corresponding authors. Xianlun Li: Tel: + 86 13910812495, E-mail: leexianlun@163.com. Hong Jiang: Tel: + 86 15811227722, E-mail: drjh68@163.com. Xianlun Li, Hong Jiang, Jiahui Li and Peng Yang conceived the original concept of the study and wrote the draft of the protocol manuscript. Other authors contributed to the design of the study. All authors approved the final manuscript.
	5b	Name and contact information for the trial sponsor page 1 Trial sponsor: Beijing Municipal Commission of Health and Family Planning Telephone: 86-10-83970661 Principal investigator: Xianlun Li: Tel: + 86 13910812495, E-mail: leexianlun@163.com.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities page 13 The funding source does not influence or comment on planned methods, protocol, data analysis, or the draft report.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) page 6,7,10-11,

		Patients will be recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who will obtain written consent from patients willing to participate in the trial. China-Japan Friendship Hospital clinical research data management platform is commissioned to generate a random sequence of 120 numbers using SAS 9.4 software. The random sequence will be put into sealed envelopes by staff not involved with the study to avoid selecting bias. Data managers from Beijing Cardiar Technology, China are responsible for the data entry and management. Two data managers perform double entry independently and proofread to ensure the data accuracy. China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organisers. All statistical analyses will be completed by Beijing Zhengyuan Technology Co., Ltd using SAS 9.4 software.
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Page 4,5 Heart failure (HF) is a complex clinical syndrome caused by abnormal cardiac structure or function which results in impaired ventricular filling or ejection ability. It is a terminal stage of

		various cardiovascular diseases, which has become the global public health problem of great concern. The prevalence of HF in the whole population is approximately 1.5%-2% and 6%-10% over 65 years of age [1]. More and more individuals are surviving an acute cardiovascular attack due to modern therapies now and the concomitant burden of chronic HF (CHF) is also increasing worldwide. At present, there are 8-10 million patients with HF in China, and the prevalence rate increases significantly with age according to China Cardiovascular report 2017[2]. The 5-year survival rate of HF patients with clinical symptoms is 50% ,similar to that of malignant tumors[1]. Repeated visits and hospitalizations of HF patients bring heavy economic burdens to individuals, families and society. Many HF patients on optimal cardiovascular medical therapy still suffer from dyspnea and exercise intolerance. In addition to medical treatment and device therapy, successful cardiac rehabilitation (CR) is a valuable intervention for improving aerobic fitness and overall health status in patients with HF. There is a growing consensus that exercise has a benefi¬cial effect on patients with cardiovascular disease, even for those with severely impaired cardiac function. HF patients can benefit from proper exercise with significant improve¬ments in exercise capacity, quality of life, and reduction in hospitalizations. Exercise training is a core component of primary and secondary prevention, which has been recommended by relevant international professional associations[3-6]. Despite its reported benefits, a limited number of HF patients attend exercise rehabilitation（ER）

		on a regular basis mainly because of poor patients′ adherence. Furthermore, improper exercise without monitoring may even cause adverse cardiovascular events such as myocardial infarction, arrhythmias and sudden death. HF-A Controlled Trial Investigating Outcomes of exercise training (HF-ACTION)[7] is the largest multicenter clinical study of ER in HF, which randomly assigned 2331 patients to either exercise training or usual care. Only Forty-two percent of subjects in their cohort completed all three of their scheduled follow-up exercise tests and 33% and 25% completed two and one of their scheduled follow-up exercise tests, respectively. Given the observed effect between higher adherence and improved outcomes, it is more important to provide cardiac ER programs which can achieve increased adherence to the exercise intervention [8]. Cardiac telerehabilitation using monitoring devices and remote communication with patients has now been used more and more in the long-term management of cardiovascular diseases outside the hospital environment. Providing objective feedback data and allowing patients to track their own progress can increase patients' self-management skills and thus improve their adherence. It is convenient and can reduce anxiety, improve the quality of life and prognosis of patients with low medical costs compared with conventional ER without monitoring [9-13].
	6b	Explanation for choice of comparators page 5 Cardiac telerehabilitation using monitoring devices and remote communication with patients has now been used more and more in the long-term management of cardiovascular diseases outside

		the hospital environment. Providing objective feedback data and allowing patients to track their own progress can increase patients' self-management skills and thus improve their adherence. It is convenient and can reduce anxiety, improve the quality of life and prognosis of patients with low medical costs compared with conventional ER without monitoring [9-13].
Objectives	7	Specific objectives or hypotheses page 5 This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness and safety of home-based phase-II ER under the guidance of remote electrocardiogram （ECG）monitoring system（REMS） in the management of CHF compared with conventional ER without monitoring.
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 5 This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness and safety of home-based phase-II ER under the guidance of remote electrocardiogram （ECG）monitoring system（REMS） in the management of CHF compared with conventional ER without monitoring.
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained page 6

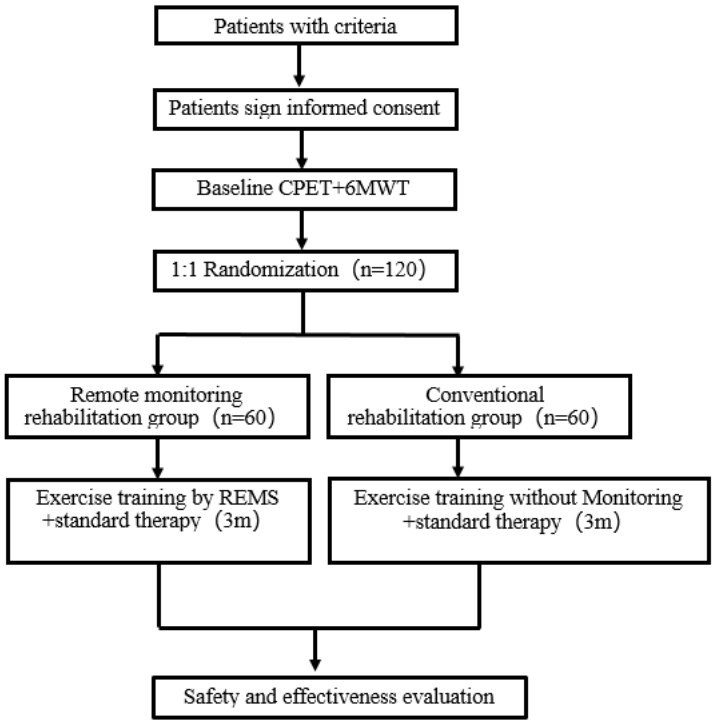
		Patients will be recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Page 6,17 Inclusion criteria: 1. Aged 18-75 years old; 2. NYHA I-III; LVEF<50% in 6 weeks before randomization; 3. in stable condition after heart failure standard drug therapy (do not need intravenous diuretics, vasoconstrictors, vasodilators or left ventricular assist device), no fluid retention, constant weight; 4. able to perform exercise rehabilitation; 5. clearly understand the content and purpose of the study and volunteer to participate in the study and sign the informed consent form. Exclusion criteria：1. exercise rehabilitation can not be carried out due to physical disability and contraindication; 2. with a contraindication to cardiopulmonary exercise test; 3. the following was happened in 3 months before admission: acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid artery or other major vascular surgery; percutaneous coronary intervention (PCI)or carotid artery angioplasty; sustained ventricular tachycardia or fibrillation; 4. coronary

		revascularization or heart transplantation is planned; 5. persistent atrial arrhythmias ; ventricular arrhythmias were not effectively controlled (using an antiarrhythmic drug or an implantable defibrillator); 6. uncorrected primary obstructive or severe regurgitant heart valve disease, restrictive or hypertrophic cardiomyopathy; 7. II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for heart failure; 8. obstructive or bronchospasm lung disease(such as asthma, bronchitis, etc) needing oral or inhaled bronchodilator or glucocorticoids therapy; 9. pregnant or lactating women and those planning to conceive during the trial; 10. cancer or other systemic diseases with an expected survival of less than 12 months; 11. other clinical trial drugs were taken or in other medical device trial within 30 days before admission; 12. unable to participate in this study after the clinical evaluation by investigators
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered page8,9 All the patients initiate an exercise training program following the principles of exercise prescription as recommended by the American College of Sports Medicine (ACSM) and the AHA. The exercise stage order can be warm-up, main exercise, and cool-down. For the warm-up and cool-down, walking or light stretching is recommended. The main exercise is walking. Exercise training initially begins in a supervised setting and then transitions to a home-based

		regimen（Table 3 and Table 4）. The supervised training phase consists of 12 supervised training sessions, with a goal of 3 sessions per week. Patients have up to 1 month to complete the 12 sessions before transition to the home exercise phase. Patients are asked to exercise 5 times per week during the home exercise phase, totally 8 weeks. Patients begin exercising at a low intensity and then increase to a moderate intensity when they are able. The trial protocol allows patients to walk independently. In the REMS group, patients wear Inticare-MC-06 ECG monitors when exercising at home to ensure that exercise intensity is within the ranges set for them and are instructed on how to monitor their own exercise training at the beginning of the trial. During the exercise, the monitor can evaluate whether patients reach the intensity and time of the preset exercise prescription according to the heart rate. If the speed is not enough or the intensity exceeds the preset value, the system can remind the patient promptly to adjust the intensity, including speed and time course, so as to ensure the patient to exercise according to the prescription. If arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. Specialists will give an analysis report. The system will give an early warning to both patients and their doctors if the arrhythmia is risky. Doctors can check the data of their patients outside hospital, know about their conditions and give advice in time. The heart rate reserve (HRR) method is used to guide exercise intensity. Peak heart rate is derived from a patient's most recent exercise test, and the resting heart rate is taken after 5 minutes of quiet seated rest. For the first 6 supervised training sessions, the training heart rate range is

		computed at 60% of the HRR (resting heart rate + 0.6 [peak heart rate-resting heart rate]). Then training intensity is increased to 70% of the HRR for the rest of the supervised exercise training sessions. For the home-based exercise training phase, patients are asked to perform 40 minutes of aerobic exercise. In the REMS training arm, the training intensity should be maintained at 60% to 70% of the HRR. While during the whole phase of the conventional rehabilitation arm, the training intensity is not monitored.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Page 8 If a cardiogram such as arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. The data will be transformed to the data center, while specialist will give an analysis for that report. The unique algorithm can analyze the data in real time and detect suspected arrhythmias, then give the alarm and transfer data to cloud platform for doctors to check and confirm the disease. In addition, when patients have chest discomfort, palpitation and dizziness, they can mark the ECG data through One-Tap Marking button and send the data for doctors to check and give corresponding diagnosis. At the end of the monitoring, a report will be provided.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

		Page 9,10 During the training phase, participants will be asked to exercise strictly according to the prescription and record each exercise process with designed cards. Investigators will make telephone reminders before each visit and then give face-to-face reminders at each study visit emphasizing the importance of adherence. Compliance of ER in subjects are expressed in rate.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Page 9 Participants in both groups will continue standard therapy for HF. The medication should remain unchanged during the trial, while the dosage should be adjusted in case of adverse events. All procedures will be determined by physicians following the clinical guidelines.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Page 10 The primary outcome is exercise capacity improvement measured by peak oxygen uptake (VO2 peak) (baseline vs 3 m). The secondary outcomes are: (1) difference in the meters walked in the 6-min Walk Test (6MWT); (2) improvement in heart function assessed by NYHA classifications; (3) improvement in echocardiographic parameters of systolic and diastolic function; (4)changes in biomarkers, including brain natriuretic peptide（BNP）/ N-terminal-pro-brain natriuretic peptide（NT-pro-BNP）and Troponin-T/I; (5) changes in major adverse cardiovascular events (MACE) including worsening HF event, HF hospitalization, myocardial infarction, stroke, revascularization and cardiovascular mortality; (6) qualitative evaluation of patients' adherence to the rehabilitation program. The investigators will also use several validated psychometric instruments to measure health-related quality of life and depression. These measurements include

		HF Symptom Scale，Minnesota Living with Heart Failure Questionnaire (MLHFQ), 36-Item Short Form Health Survey (SF-36), Beck Depression Inventory-II (BDI-II) and General Self-Efficacy Scale (GSE).
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended Figure1 

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Page 6 The target enrollment for the trial is 120 patients. A total of 500 patients with HF (NYHA grade I-III) are treated in our hospital every year， which can be used as a screening sample. Calculated according to the lower screening rate (50%) and the designed entry criteria, the sample size that can be completed is estimated to be 100 patients. Referring to the previous foreign literature, the compliance of ER in 3 months is 70-80%. The initial screening sample size of this study is at least 120 cases, 60 cases in each group.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Page 6 Screening will continue until the target population is achieved. A recruitment advertisement has also been utilized in our hospital.
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions Page 7 China-Japan Friendship Hospital clinical research data management platform is commissioned to

		generate a random sequence of 120 numbers using SAS 9.4 software. The random sequence will be put into sealed envelopes by staff not involved with the study to avoid selecting bias.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Page 7 After providing informed consent and undergoing baseline testing (echocardiogram and CPET), patients are randomized in a 1:1 ratio to either REMS rehabilitation group or the conventional rehabilitation group according to the time order of the patients' entry. Allocation concealment will be ensured and the randomization code will not be released until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. Researchers involved in participants' assessments will be blinded to treatment allocation.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Page 6,7 China-Japan Friendship Hospital clinical research data management platform is commissioned to generate a random sequence of 120 numbers using SAS 9.4 software. Patients will be recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who will obtain written consent from patients willing to participate in the trial.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how

		Page 10,11 Researchers involved in participants' assessments will be blinded to treatment allocation. All individuals involved in data management and analysis will be blinded to treatment allocation.
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Page10,11 All patients' data will be recorded by trained clinical researchers using a standardized case report form (CRF). Original data should be recorded timely and accurately. Laboratory reports copies should also be kept. All CRFs will be stored in locked file cabinets in areas with limited access. All laboratory specimens will be identified by a coded number to maintain participant confidentiality. Data managers from Beijing Cardiar Technology, China are responsible for the data entry and management. Two data managers perform double entry independently and proofread to ensure the data accuracy. China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organizers. All individuals involved in data management and analysis will be blinded to treatment allocation. Principal investigators will have direct access to data sets. Data dispersed to project team members will be blinded of any identifying participant information.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

		Page 9,10 During the training phase, participants will be asked to exercise strictly according to the prescription and record each exercise process with designed cards. Investigators will make telephone reminders before each visit and then give face-to-face reminders at each study visit emphasizing the importance of adherence.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Page10,11 All patients' data will be recorded by trained clinical researchers using a standardized case report form (CRF). Original data should be recorded timely and accurately. Laboratory reports copies should also be kept. All CRFs will be stored in locked file cabinets in areas with limited access. All laboratory specimens will be identified by a coded number to maintain participant confidentiality. Data managers from Beijing Cardiar Technology, China are responsible for the data entry and management. The database is established by PHP language under Linux system. Two data managers perform double entry independently and proofread to ensure the data accuracy. China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organizers. All individuals involved in data management and analysis will be blinded to treatment allocation. Principal investigators will have direct access to data sets. Data dispersed to project team members will be blinded of any identifying participant information.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Page 11,12 Continuous variables will be presented as the mean ±standard deviation (SD), median or interquartile range (IQR). Baseline characteristics of the cohort will be summarized using

		descriptive statistics. Whether imbalances exist will be analyzed between groups. Comparison of numerical variables between the two groups is made using Student's t-test for independent samples when normally distributed. Categorical variables will be described as frequencies and percentages and compared using $\chi 2$ test. Mann-Whitney U test will be used if data are not normally distributed. Analysis of outcomes will be conducted according to the intention-to-treat (ITT) principle. We will use three analysis sets: full analysis set（FAS）, per protocol set（PPS）and safety set. The FAS includes all patients randomized, and the PPS consists of all patients who complete the treatment protocol. The safety set consists of patients who receive at least one treatment with safety records after randomization. Dropouts will be included in the analysis by modern imputation methods for missing data. All statistical tests will be 2-tailed. $P<0.05$ is considered statistically significant. All statistical analyses will be completed by Beijing Zhengyuan Technology Co., Ltd using SAS 9.4 software.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) page 12 Dropouts will be included in the analysis by modern imputation methods for missing data.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Page 11,12 Analysis of outcomes will be conducted according to the intention-to-treat (ITT) principle. We will use three analysis sets: full analysis set（FAS）, per protocol set（PPS）and safety set. The FAS includes all patients randomized, and the PPS consists of all patients who complete the treatment protocol. The safety set consists of patients who receive at least one treatment with safety records after randomization.
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure;

		statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Page11 China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organizers.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Page 11 All adverse events that occurred during the 3-month study period will be reported in the final paper. A serious adverse event is defined as any untoward medical occurrence resulting in hospitalization or which results in a life-threatening problem, death, or disability. Adverse events will be defined as any untoward occurrences in study participants, potentially related to implementation of the study protocol. All serious and unexpected adverse events will be reported to the Ethics Committee as required.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor N/A
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

		Page 3 This study was approved by Ethics Committee of China-Japan Friendship Hospital for Clinical Research（No. 2018-55-K39）.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Page 5 If there is any amendment to the protocol, approval must be sought again from the Ethics Committee.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 6 Patients will be recruited consecutively from the outpatient clinic of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who will obtain written consent from patients willing to participate in the trial.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Page 11

		All CRFs will be stored in locked file cabinets in areas with limited access. All laboratory specimens will be identified by a coded number to maintain participant confidentiality.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 14 The authors declare that they have no competing interests.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Page 11 Principal investigators will have direct access to data sets. Data dispersed to project team members will be blinded of any identifying participant information.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care and for compensation to those who suffer harm from trial participation N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Page 3 The results of this study will be disseminated via peer-reviewed publications and presentations at conferences.
	31b	Authorship eligibility guidelines and any intended use of professional writers N/A Topics suggested for publication will be circulated to the principal investigators.

		No intended use of professional writers. N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code No later than 3 years after the collection of the 3m postrandomization interviews, we will deliver a deidentified data set to an appropriate data archive for sharing purposes. N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates A Chinese version of informed consent (V1.1, 20180208) has been reviewed and approved by the Ethics Committee of China-Japan Friendship Hospital for Clinical Research. N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A

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Effects of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure（HERE-CHF）：Study Protocol for a Randomized Controlled Trial

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Effects of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure （HERE-CHF）：Study Protocol for a Randomized Controlled Trial

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Abstract

Introduction

Patients with chronic heart failure (CHF) can benefit from exercise rehabilitation (ER) with significant improvements in exercise capacity, quality of life, and reduction in hospitalizations. Despite its reported benefits, only a small number of patients with CHF attend ER due to poor adherence and improper exercise may even lead to adverse events. Remote electrocardiogram monitoring system (REMS) has the potential to overcome these obstacles. We hypothesize that home-based cardiac ER using REMS in CHF patients is effective compared with conventional ER without monitoring.

Methods and Analysis

This study is a prospective, randomized, parallel controlled clinical trial designed to evaluate the effectiveness of home-based phase-II ER with REMS in the treatment of CHF with a target enrollment of 120 patients 【Left Ventricular Ejection Fraction <50%, New York Heart Association (NYHA) classes I to III】. Patients are randomized to either REMS rehabilitation group or conventional rehabilitation group in a 1:1 ratio. All patients start an exercise training in a supervised setting and then transition to a home-based regimen. The supervised training phase consists of 12 supervised training sessions, 3 sessions per week for 4 weeks. During the home exercise phase, patients exercise 5 times per week for 8 weeks. In the REMS group, patients wear monitors during exercise to ensure that exercise intensity is within the set ranges. REMS will also detect risky arrhythmia and alert the patients and their doctors on time. The training intensity is not monitored in the conventional rehabilitation group. The primary outcome is exercise capacity improvement measured by peak oxygen uptake (VO_2 peak) (baseline vs 3 m). Secondary outcomes include 6-min Walk Test (6MWT), NYHA classes, echocardiographic parameters, cardiac biomarkers, major adverse cardiovascular events (MACE), quality of life, psychological well-being and patients' adherence to the rehabilitation program.

Ethics and Dissemination

This study was approved by Ethics Committee of China-Japan Friendship Hospital for Clinical Research（No. 2018-55-K39）. The results of this study will be disseminated via peer-reviewed publications and presentations at conferences.

Clinical trial registration number

ChiCTR-RNR-17012446

Strengths and limitations of this study

1. The wearable monitor used in this study is portable, which can evaluate patients' exercise intensity based on their heart rate and then remind them to exercise appropriately.
2. The REMS used here can detect arrhythmia and provide an early warning to both the exercising patients and their doctors to further reduce risks.
3. Our cardiac ER program is home-based and convenient for CHF patients compared with facility-based ER, which may provide new insights into cardiac telerehabilitation in patients with CHF.
4. The main limitation of this single-center study is the small sample size.
5. A long-term follow-up may also be needed and extending the exercise out to 6 months may give us better data on adherence.

Keywords: Cardiac exercise rehabilitation, Telerehabilitation, Chronic heart failure, Remote Electrocardiogram Monitoring System

Introduction

Heart failure (HF) is a complex clinical syndrome caused by abnormal cardiac structure or function which results in impaired ventricular filling or ejection ability. It is a terminal stage of various cardiovascular diseases, which has become the global public health problem of great concern. The prevalence of HF in the entire population is approximately 1.5%-2% and 6%-10% over 65 years of age [1]. Nowadays, due to modern therapies, more and more people are spared from acute cardiovascular attacks and the concomitant burden of chronic HF (CHF) is also increasing globally. According to the 2017 China Cardiovascular report[2], there are currently 8-10 million HF patients in China, and the prevalence rate increases significantly with age. The 5-year survival rate of HF patients with clinical symptoms is 50% , similar to that of malignant tumors[1]. For HF patients, repeated visits and hospitalizations place heavy financial burdens on individuals, families and society.

Many HF patients on optimal cardiovascular medical therapy still suffer from dyspnea and exercise intolerance. In addition to medical treatment and device therapy, successful cardiac rehabilitation (CR) is a valuable intervention for improving aerobic fitness and overall health status in patients with HF. HF patients can benefit from proper exercise with significant improvements in exercise capacity, quality of life, and reduction in hospitalizations[3-6]. Exercise training is a core component of primary and secondary prevention for HF, which has been recommended by relevant international professional associations[3-6].

Despite its reported benefits, a limited number of HF patients regularly participate in exercise rehabilitation (ER) , primarily because of poor patients' adherence. In addition, inappropriate exercise that is not monitored may even cause adverse cardiovascular events such as myocardial infarction, arrhythmias and sudden death. HF-A Controlled Trial Investigating Outcomes of exercise training (HF-ACTION)[7] is the largest multicenter clinical study of ER in HF, which randomly assigned 2331 patients to either exercise training or usual care. Only 42% of the subjects in their cohort completed all three scheduled follow-up exercise tests and 33% and 25% completed

two and one of their scheduled follow-up exercise tests, respectively. Given the observed effect between higher adherence and improved outcomes, it is more important to provide cardiac ER programs which can achieve increased adherence to the exercise intervention [8].

Cardiac telerehabilitation using monitoring devices and remote communication with patients is now increasingly used for long-term management of cardiovascular diseases outside the hospital environment. Providing objective feedback data and allowing patients to track their own progress can improve patients' self-management skills and thereby improve their adherence. It is convenient and can reduce anxiety, improve the quality of life and prognosis of patients with low medical costs compared with conventional ER without monitoring [9-13].

This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness and safety of home-based phase-II ER under the guidance of remote electrocardiogram (ECG) monitoring system (REMS) in the management of CHF compared with conventional ER without monitoring. This paper describes the design and rationale of the **HERE-CHF** trial.

Methods/design

Design

A flow chart of the study design is shown in Figure 1. The protocol is constructed and presented in accordance with the recommendations for Interventional Trials (SPIRIT) [14]. The study protocol (V1.1, 20180208) and informed consent documents (V1.1, 20180208) have been reviewed and approved by the Ethics Committee of China-Japan Friendship Hospital for Clinical Research. If there is any amendment to the protocol, approval must be sought again from the Ethics Committee. The study strategy has been registered on the website of Chinese Clinical Trial Registry (ChiCTR-RNR-17012446, registered on 22 August 2017), and the trial will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Eligibility and recruitment

Patient selection criteria are listed in Table 1. Patients must have a systolic cardiac

dysfunction documented from a baseline echocardiogram 【LV ejection fraction (LVEF) <50%】and are in stable conditions【New York Heart Association (NYHA) classes I to III】within 6 weeks prior to randomization. According to the American College of Cardiology(ACC)/American Heart Association (AHA) HF guidelines, stable optimal drug therapies including β blockers, diuretics, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) and aldosterone receptor antagonists for 6 weeks before enrollment is strongly advocated. If patients are not treated with optimal medical therapy, then trial personnel must document the underlying reason (eg, drug intolerance).

Patients enrollment began in April 2018. Patients were recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who had obtained written consent from patients who were willing to participate in the trial. Screening will continue until the target population is achieved. A recruitment advertisement has also been utilized in our hospital. No financial incentives were provided to the attending physicians or patients for enrollment.

Sample size

The target number of participants in the trial is 120 subjects. A total of 500 HF patients (NYHA grade I-III) are treated in our hospital each year and can be used as a screening sample. Based on the lower screening rate (50%) and the designed entry criteria, the sample size that can be completed is estimated to be 100 patients. With reference to previous foreign literature, the compliance of ER within 3 months is 70-80%. The study will enroll at least 120 subjects, 60 subjects in each group.

Exercise testing

The prerandomization cardiopulmonary exercise testing (CPET) is used to determine whether patients can exercise safely in according with the guidelines of the American Association of Cardiovascular and Pulmonary Rehabilitation, including checking for abnormal blood pressure responses, early ischemic changes, and significant arrhythmias. Exercise testing is repeated 3 month after randomization for all patients.

The primary method used for exercise testing is cycling, consistent with AHA guidelines and with other trials that have assessed exercise capacity in patients with HF.

Randomization and binding

The clinical research data management platform of China-Japan Friendship Hospital was commissioned to generate a random sequence of 120 numbers using SAS 9.4 software. The random sequence is placed into a sealed envelope by a staff member who is not involved in the study to avoid selection bias. After providing informed consent and undergoing baseline testing (echocardiogram and CPET), patients are randomly assigned to the REMS rehabilitation group or the conventional rehabilitation group in a 1:1 ratio based on the patient's admission time. Allocation concealment is ensured and the randomization code will not be released until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. Researchers involved in participants' assessments are blinded to treatment allocation.

Trial structure

The trial structure of the study is described in the Table 2.

REMS

Inticare-MC-06 wearable ECG monitor (Elephant Medical Electronic Technology Co., Ltd, Jining, China), approved by Food and Drug Administration in Shandong province of China (Certificate No. Shandong Medical Device Registration Approval 20172210878) is a medical-grade portable cardiac monitor and looks like a smaller "Band-Aid" that can collect 48 hours of single-lead ECG data. It can provide cardiac care service through a "Hardware + Software+ Cloud + Doctor" program, and support arrhythmia automatic trigger and One-Tap SOS. Inticare-MC-06 heart health monitor solution consists of five parts: a wearable ECG monitor, mobile terminals (such as smart phones), Cardiac Healthcare Cloud Service platform of Elephant Medical (Tianjin AI-Life Medical Technology Co., Ltd, China), cardiologists and monitoring reports, supported by Tianjin Institute of Internet of Things Technology. The wearable ECG monitor is pasted on the chest through one-piece electrodes and

transfers the ECG data to the smart phone application of cloud service platform (Elephant Heart Health) via bluetooth smart technology. If an electrocardiogram such as arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. The data will be transformed to the data center, and the specialist will analyze that report. The unique algorithm analyzes the data in real time and detects suspicious arrhythmias, then sends out alerts and transfers data to cloud platform for doctors to check and confirm the disease. In addition, when patients have chest discomfort, palpitation and dizziness, they can mark the ECG data through One-Tap Marking button and send the data for doctors to check and give corresponding diagnosis. At the end of the monitoring, a report will be provided.

Interventions

All the patients initiate an exercise training program in accordance with the principles of exercise prescription recommended by the American College of Sports Medicine (ACSM) and the AHA. The sequence of the exercise phase can be warm-up, main exercise, and cool-down. For the warm-up and cool-down, walking or light stretching is recommended. The main exercise is walking. Exercise training initially begins in a supervised setting and then transitions to a home-based regimen（Table 3 and Table 4）. The supervised training phase consists of 12 supervised training sessions, with a goal of 3 sessions per week. It takes up to 1 month for patients to complete the 12 sessions before transition to the home exercise phase. Patients are required to exercise 5 times per week during the home exercise phase for a total of 8 weeks. Patients begin exercising at a low intensity and then increase to a moderate intensity when they are able to do so. The trial protocol allows patients to walk independently.

In the REMS group, patients wear Inticare-MC-06 ECG monitors while exercising at home to ensure that exercise intensity is within their set ranges and are instructed on how to monitor their own exercise training at the beginning of the trial. During the exercise, the monitor can evaluate whether patients have reached the intensity and time of the preset exercise prescription based on the heart rate. If the speed is not enough or

the intensity exceeds the preset value, the system can remind the patient promptly to adjust the intensity, including speed and time course, to ensure that the patient to exercise based on the prescription. If arrhythmia occur during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. Specialists will give an analysis report. The system will give an early warning to both patients and their doctors if the arrhythmia is risky. Doctors can check data from patients outside hospital to understand their conditions and provide timely advice.

The heart rate reserve (HRR) method is used to guide exercise intensity. Peak heart rate is derived from a patient's most recent exercise test, and the resting heart rate is taken after a quiet seated rest for 5 minutes. For the first 6 supervised training sessions, the training heart rate range is calculated as 60% of the HRR (resting heart rate + 0.6 [peak heart rate-resting heart rate]). Then training intensity is increased to 70% of the HRR for the rest of the supervised exercise training sessions. For the home-based exercise training phase, patients are asked to perform 40 minutes of aerobic exercise. In the REMS training arm, the training intensity should be maintained at 60% to 70% of the HRR. The training intensity is not monitored during the entire phase of the conventional rehabilitation arm..

Concomitant treatment

Participants in both groups continue to receive standard treatment for HF. The medication should remain unchanged during the trial and the dosage should be adjusted in the event of adverse events. All procedures are determined by physicians following the clinical guidelines.

Adherence

During the training phase, participants are required to exercise in strict accordance with the prescription and use the designed cards to record each exercise process. Investigators make telephone reminders before each visit and then provide face-to-face reminders on each study visit to emphasize the importance of adherence. Compliance of ER in subjects are expressed in rate.

Outcome assessments

The primary outcome is an improvement in exercise capacity measured by peak oxygen uptake (VO_2 peak) (baseline vs 3 m). The secondary outcomes are: (1) difference in the meters walked in the 6-min Walk Test (6MWT); (2) improvement in heart function assessed by NYHA classifications; (3) improvement in echocardiographic parameters of systolic and diastolic function; (4)changes in biomarkers, including brain natriuretic peptide（BNP）/ N-terminal-pro-brain natriuretic peptide（NT-pro-BNP）and Troponin-T/I; (5) changes in major adverse cardiovascular events (MACE) including worsening HF event, HF hospitalization, myocardial infarction, stroke, revascularization and cardiovascular mortality; (6) qualitative evaluation of patients' adherence to the rehabilitation program. The investigators also use several validated psychometric instruments to measure health-related quality of life and depression. These measurements include HF Symptom Scale，Minnesota Living with Heart Failure Questionnaire (MLHFQ), 36-Item Short Form Health Survey (SF-36), Beck Depression Inventory-II (BDI-II) and General Self-Efficacy Scale (GSE). Researchers involved in participants' assessments will be blinded to treatment allocation.

Withdrawal

According to Ethics Committee of Clinical Research legislations of China-Japan Friendship Hospital, we inform the patients about their rights as subjects in a scientific trial and about their rights to terminate. We do this to allow patients to fully consider participation thoroughly to reduce their likelihood of dropping out of the study. Patients may withdraw from the trial at their own request or at the request of their legal representative at any time.

Data collection, management, and analysis

All patients' data are recorded by trained clinical researchers using a standardized case report form (CRF). Raw data should be recorded in timely and accurate manner. Copies of laboratory reports should also be kept. All CRFs are stored in locked file cabinets in areas with limited access. All laboratory specimens are identified by a coded number to maintain participant confidentiality. Data administrators from Cardiar Technology in Beijing, China are responsible for the data entry and management. The database was

built using PHP language under Linux system. Two data managers independently perform dual input and proofreading to ensure data accuracy. The clinical research data management platform of China-Japan Friendship Hospital is responsible for data monitoring, which is independent of the study organizers. All individuals involved in data management and analysis are blinded to treatment allocation. Principal investigators have direct access to data sets. Data dispersed to project team members are blinded of any identifying participant information.

Adverse events monitoring

All adverse events that occurred during the 3-month study period will be reported in the final paper. A serious adverse event is defined as any untoward medical occurrence resulting in hospitalization or which results in a life-threatening problem, death, or disability. Adverse events are defined as any untoward occurrences in study participants, potentially related to implementation of the study protocol. All serious and unexpected adverse events will be reported to the Ethics Committee as required.

Statistical analysis

Continuous variables will be presented as the mean ±standard deviation (SD), median or interquartile range (IQR). Baseline characteristics of the cohort will be summarized using descriptive statistics. Whether there are imbalances will be analyzed between groups. When normally distributed, independent samples will be compared for numerical variables between the two groups using Student's t-test. The categorical variables described as frequencies and percentages will be compared using Chi-square test. Mann-Whitney U test will be used if data are not normally distributed.

Analysis of outcomes will be conducted based on the intention-to-treat (ITT) principle. We will use three sets of analysis: full analysis set（FAS）, per protocol set（PPS）and safety set. The FAS includes all randomized patients, and the PPS consists of all patients who complete the treatment protocol. The safety set consists of patients who receive at least one treatment with safety records after randomization. Dropouts will be included in the analysis by modern imputation methods for missing data.

All statistical tests will be 2-tailed. $P<0.05$ is considered statistically significant. All

statistical analyses will be completed by Beijing Zhengyuan Technology Co., Ltd using SAS 9.4 software.

Patient and Public Involvement (PPI)

During the study design period, CHF patients and their relatives were invited to participate in surveys and discussions, which allowed us to know their strong desire in ER, especially home-based telerehabilitation. We also selected several patients to use the monitor, which helped us to identify problems in application. In addition, we invited medical specialists including cardiologists, rehabilitation therapists and statistical analysts to discuss the study design and revise the intervention method and outcome measures. The results of our study will be disseminated to PPI representatives and study participants who wish to be notified.

Discussion

HERE-CHF evaluates the effect of cardiac telerehabilitation intervention that combines modern technology (sensor technology, internet and remote consultation) with evidence-based ER guidance strategies , including prevention of adverse events during exercising. The objective of this study is to investigate whether home-based cardiac ER using REMS is superior to conventional ER without monitoring in CHF patients. We hypothesize that this intervention will improve physical activity levels and quality of life.

Home-based CR is a method to increase the ER participation rate in HF patients. Whether exercise prescription can be performed effectively and the safety in exercise are two main issues in home-based ER. While exercise intensity is the key of exercise prescription because the exercise must be appropriate. Heart rate is the most important factor to monitor the patient's exercise intensity. Our wearable ECG monitor can evaluate whether patients reach the intensity based on the heart rate and promptly alert the patients to ensure that exercise intensity is within the preset range. REMS will also detect risky arrhythmia and provide an early warning to both the patients and their doctors, which can encourage patients to overcome fear and adhere to exercise. The use of our REMS offers a prospect for the delivery and expansion of home-based cardiac

ER programs in HF patients beyond the supervised setting and will help to increase adherence, reduce risk factors and improve benefit-cost ratio ，which may further enhance the effectiveness of ER.

CPET can be used to evaluate patient exercise capacity and exertional symptoms and can provide numerous physiologic parameters. Multiple CPET-derived variables have been assessed for their association with mortality in systolic HF patients and peak VO_2 is shown to be the strongest predictor of mortality [15]. Therefore，we select it as the primary outcome in **HERE-CHF**. The 6MWT is chosen as a secondary outcome due to its useful prognostic information similar to peak VO_2[16]. 6MWT is less expensive and much more convenient in comparison to the nontrivial costs of CPET with its distinctive value as a measure of routine activity. Quality of life and psychological state are important in the evaluation of home-based ER, which are also included in our study.

Conclusion

The **HERE-CHF** study will provide new insights into the effect of home-based cardiac ER guided by REMS. Our REMS will help to increase adherence and reduce risk factors for HF patients, which may further enhance the effectiveness of ER.

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Contributors

Xianlun Li, Hong Jiang, Jiahui Li and Peng Yang conceived the original concept of the study, registered the trial and wrote the draft of the protocol manuscript. Dongliang Fu, Xiaojun Ye, Lifang Zhang, Gang Chen, Yiyun Yang, He Luo, Li Chen，Mingjing Shao，Chunyan Li, Yi Liu and Ying Zhou contributed to the design of the study. All the authors read and discussed the manuscript, and approved the final version.

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Competing interests

The authors declare that they have no competing interests.

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Table 1. HERE-CHF trial inclusion and exclusion criteria

Inclusion criteria

1. Aged 18-75 years old;
2. NYHA I-III; LVEF<50% in 6 weeks before randomization;
3. in stable condition after heart failure standard drug therapy (do not need intravenous diuretics, vasoconstrictors, vasodilators or left ventricular assist device), no fluid retention, constant weight;
4. able to perform exercise rehabilitation;
5. clearly understand the content and purpose of the study and volunteer to participate in the study and sign the informed consent form.

Exclusion criteria

1. exercise rehabilitation can not be carried out due to physical disability and contraindication;
2. with a contraindication to cardiopulmonary exercise test;
3. the following was happened in 3 months before admission: acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid artery or other major vascular surgery; percutaneous coronary intervention (PCI)or carotid artery angioplasty; sustained ventricular tachycardia or fibrillation;
4. coronary revascularization or heart transplantation is planned;
5. persistent atrial arrhythmias ; ventricular arrhythmias were not effectively controlled (using an antiarrhythmic drug or an implantable defibrillator);
6. uncorrected primary obstructive or severe regurgitant heart valve disease, restrictive or hypertrophic cardiomyopathy;
7. II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for heart failure;
8. obstructive or bronchospasm lung disease(such as asthma, bronchitis, etc) needing oral or inhaled bronchodilator or glucocorticoids therapy;
9. pregnant or lactating women and those planning to conceive during the trial;
10. cancer or other systemic diseases with an expected survival of less than 12 months;
11. other clinical trial drugs were taken or in other medical device trial within 30 days before admission;
12. unable to participate in this study after the clinical evaluation by investigators.

Table 2 Trial structure of the study

Time / Assessment	Screening (-14~-1d)	Exercise Rehabilitation in Clinic			Exercise Rehabilitation at Home	
		T0 Visit 1 Baseline	T1 Visit 2 2nd weekend	T2 Visit 3 4th weekend	T3 Visit 4 8th weekend	T4 Visit 5 12th weekend
medical history	√					
Inclusion/Exclusion Form	√					
Consent Form	√					
Comorbidity	√	√	√	√	√	√
Concomitant medication	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√
Troponin T/I		√				√
BNP/NT-proBNP		√				√
Electrocardiogram	√	√		√	√	√
Holter	√					√
NYHA classification	√	√		√	√	√
Echocardiography	√	√				√
CPET	√					√
6MWT		√				√
Heart failure symptom scale		√				√

MLHFQ		√				√
SF-36		√				√
BDI-II		√				√
GSE		√				√
Compliance				√	√	√
Adverse event			√	√	√	√
Monitor and APP training		√				

The time window for each visit is ±3d. MLHFQ: Minnesota Living with Heart Failure Questionnaire. SF-36: 36-Item Short Form Health Survey. BDI-II: Beck Depression Inventory. GSE: General Self-Efficacy Scale.

Table 3. Exercise training program in remote ECG monitoring system rehabilitation group

Training phase	Location	week	Weekly sessions	Aerobic duration (min)	Intensity (percentage of HRR)	Mode of exercise
Initial,supervised by Rehabilitation specialist	Clinic	2	3	15-30	60	walk
supervised by Rehabilitation specialist	Clinic	2	3	15-30	70	walk
Supervised by remote ECG monitoring	home	8	5	40	60-70	walk

Table 4. Exercise training program in conventional rehabilitation group without monitoring

Training phase	Location	week	Weekly sessions	Aerobic duration (min)	Intensity (percentage of HRR)	Mode of exercise
Initial, supervised by Rehabilitation specialist	Clinic	4	3	15-30	without monitoring	walk
Symptom-Limited, self-adaption	home	8	5	40	without monitoring	walk

Legends

Figure 1 Study flow chart. CPET: cardiopulmonary exercise testing. 6MWT: 6-min Walk Test. REMS：remote electrocardiogram monitoring system.

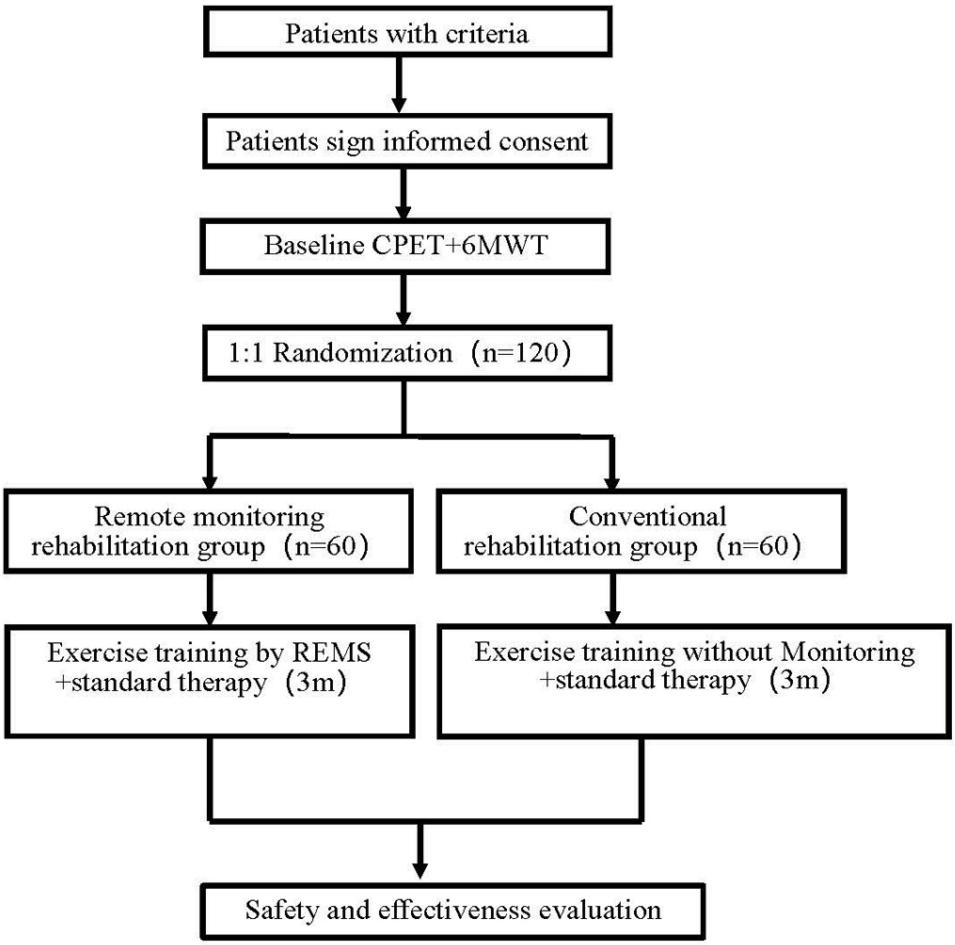

Figure 1 Study flow chart. CPET: cardiopulmonary exercise testing. 6MWT: 6-min Walk Test. REMS : remote electrocardiogram monitoring system.

90x90mm (300 x 300 DPI)

SPIRIT 2013 checklist

Section/item	ItemNo	Information
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym page 1 Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure (HERE-CHF) : Study Protocol for a Randomized Controlled Trial page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page 3 www.chictr.org.cn ChiCTR-RNR-17012446
	2b	All items from the World Health Organization Trial Registration Data Set N/A Registration number： ChiCTR-RNR-17012446 Date of Last Refreshed on： 2017/8/22 10:09:47 Registration Status： 1008001 Prospective registration Public title： An Exploratory Clinical Study on Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart

		Failure			
		Scientific title：	An Exploratory Clinical Study on Effect of Home-based Cardiac Exercise Rehabilitation with Remote Electrocardiogram Monitoring in Patients with Chronic Heart Failure		
		Applicant：	Li Jiahui	Study leader：	Li Xianlun
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		Applicant address：	2 Yinghua Street East, Chaoyang District, Beijing, China，100029	Study leader's address：	2 Yinghua Street East, Chaoyang District, Beijing, China ,100029
		Applicant's institution：	China-Japan Friendship Hospital		

		Primary sponsor：China-Japan Friendship Hospital Primary sponsor's address：2 Yinghua Street East, Chaoyang District, Beijing, China Source(s) of funding：Self-financing Target disease：heart faliure Study type：Relative factors research Study phase：New Treatment Measure Clinical Study Objectives of Study： To evaluate the efficacy and safety of home-based cardiac exercise rehabilitation with remote electrocardiogram(ECG) monitoring in patients with chronic heart failure(NYHA classification I-III).To demonstrate that home-based exercise rehabilitation with remote ECG monitoring has the advantages of standardization and easy implementation compared with traditional exercise rehabilitation. Study design： Randomized parallel controlled trial Inclusion criteria (1) Aged 18-75 years old, male or female; (2) chronic heart failure (NYHA classification I-III); LVEF<50% in 6 weeks before randomization; (3) in stable condition after heart failure standard

		drug therapy (do not need intravenous diuretics, vasoconstrictors, vasodilators or left ventricular assist device),no fluid retention,constant weight; (4) able to perform exercise rehabilitation; (5) clearly understand the content and purpose of the study and volunteer to participate in the study and sign the informed consent form. Exclusion criteria： 1. exercise rehabilitation can not be carried out due to physical disability and contraindication; 2. with a contraindication to cardiopulmonary exercise test; 3. the following was happened in 3 months before admission: acute coronary syndrome, stroke, transient ischemic attack;cardiac,carotid artery or other major vascular surgery;percutaneous coronary intervention (PCI)or carotid artery angioplasty;sustained ventricular tachycardia or fibrillation; 4. coronary revascularization or heart transplantation is planned; 5. ventricular arrhythmias were not effectively controlled (using an antiarrhythmic drug or an implantable defibrillator); 6. uncorrected primary obstructive or severe regurgitant heart valve disease,restrictive or hypertrophic cardiomyopathy; 7. II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for heart failure; 8. obstructive or bronchospasm lung disease(such as asthma, bronchitis,etc) needing oral or inhaled bronchodilator or glucocorticoids therapy; 9. pregnant or lactating women and those planning to conceive during the trial; 10. cancer or other systemic diseases with an expected survival of less than 12 months; 11. other clinical trial drugs were taken or in other medical device trial within 30 days before admission; 12. unable to participate in this study after the clinical evaluation by

		investigators. Study execute time：From2018/01/01 To 2020/12/31 Interventions： Remote electrocardiogram monitoring group Sample size：60 Control group without monitoring Sample size：60 Countries of recruitment and research settings：China-Japan Friendship Hospital,China Level of the institution：Tertiary A hospital Outcomes：VO2Peak，6 minute walk distance，left ventricular ejection fraction, blood test Randomization Procedure (please state who generates the random number sequence and by what method)： The clinical data management platform of China-Japan Friendship Hospital is commissioned to create SAS 9.4 software to generate random concealment table tables. Masked envelopes will be produced by random concealment and participants are admitted by 1:1 random principle. The time of sharing IPD：Within six months after the trial complete The way of sharing IPD″(include metadata and protocol, If use web-based public database, please

		provide the url)：Publish original data by June 2021 in the form of meetings, speeches or articles.
Protocol version	3	Date and version identifier page 5 20180208 V1.1
Funding	4	Sources and types of financial, material, and other support page 13 This work is financially supported by China Capital Health Development Research Special Fund（2018-2-4064）. Inticare-MC-06 ECG monitors are provided by Tianjin AI-Life Medical Technology Co.，Ltd, China. The funding source does not influence or comment on planned methods, protocol, data analysis, or the draft report.
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors page1, 13 Jiahui Li1*, Peng Yang2*, Dongliang Fu2, Xiaojun Ye1, Lifang Zhang1, Gang Chen3, Yiyun Yang1, He Luo1, Li Chen4，Mingjing Shao2，Chunyan Li2, Yi Liu2，Ying Zhou1, Hong Jiang2※, Xianlun Li1,2※ 1Department of Cardiology, China-Japan Friendship Hospital, Beijing 100029, China; 2Department of Integrative Cardiology, China-Japan Friendship Hospital, Beijing 100029, China; 3Department of Rehabilitation, China-Japan Friendship Hospital, Beijing 100029, China; 4Phase I Clinical Ward of Clinical Trial Research Center, China-Japan Friendship Hospital, Beijing 100029, China.

		※Correspondence: Xianlun Li and Hong Jiang are both corresponding authors. Xianlun Li: Tel: + 86 13910812495, E-mail: leexianlun@163.com. Hong Jiang: Tel: + 86 15811227722, E-mail: drjh68@163.com. Xianlun Li, Hong Jiang, Jiahui Li and Peng Yang conceived the original concept of the study and wrote the draft of the protocol manuscript. Other authors contributed to the design of the study. All authors approved the final manuscript.
	5b	Name and contact information for the trial sponsor page 1 Trial sponsor: Beijing Municipal Commission of Health and Family Planning Telephone: 86-10-83970661 Principal investigator: Xianlun Li: Tel: + 86 13910812495, E-mail: leexianlun@163.com.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities page 13 The funding source does not influence or comment on planned methods, protocol, data analysis, or the draft report.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) page 6,7,10-11,

		Patients will be recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who will obtain written consent from patients willing to participate in the trial. China-Japan Friendship Hospital clinical research data management platform is commissioned to generate a random sequence of 120 numbers using SAS 9.4 software. The random sequence will be put into sealed envelopes by staff not involved with the study to avoid selecting bias. Data managers from Beijing Cardiar Technology, China are responsible for the data entry and management. Two data managers perform double entry independently and proofread to ensure the data accuracy. China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organisers. All statistical analyses will be completed by Beijing Zhengyuan Technology Co., Ltd using SAS 9.4 software.
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Page 4,5 Heart failure (HF) is a complex clinical syndrome caused by abnormal cardiac structure or function which results in impaired ventricular filling or ejection ability. It is a terminal stage of

		various cardiovascular diseases, which has become the global public health problem of great concern. The prevalence of HF in the whole population is approximately 1.5%-2% and 6%-10% over 65 years of age [1]. More and more individuals are surviving an acute cardiovascular attack due to modern therapies now and the concomitant burden of chronic HF (CHF) is also increasing worldwide. At present, there are 8-10 million patients with HF in China, and the prevalence rate increases significantly with age according to China Cardiovascular report 2017[2]. The 5-year survival rate of HF patients with clinical symptoms is 50% ,similar to that of malignant tumors[1]. Repeated visits and hospitalizations of HF patients bring heavy economic burdens to individuals, families and society. Many HF patients on optimal cardiovascular medical therapy still suffer from dyspnea and exercise intolerance. In addition to medical treatment and device therapy, successful cardiac rehabilitation (CR) is a valuable intervention for improving aerobic fitness and overall health status in patients with HF. There is a growing consensus that exercise has a benefi¬cial effect on patients with cardiovascular disease, even for those with severely impaired cardiac function. HF patients can benefit from proper exercise with significant improve¬ments in exercise capacity, quality of life, and reduction in hospitalizations. Exercise training is a core component of primary and secondary prevention, which has been recommended by relevant international professional associations[3-6]. Despite its reported benefits, a limited number of HF patients attend exercise rehabilitation（ER）

		on a regular basis mainly because of poor patients′ adherence. Furthermore, improper exercise without monitoring may even cause adverse cardiovascular events such as myocardial infarction, arrhythmias and sudden death. HF-A Controlled Trial Investigating Outcomes of exercise training (HF-ACTION)[7] is the largest multicenter clinical study of ER in HF, which randomly assigned 2331 patients to either exercise training or usual care. Only Forty-two percent of subjects in their cohort completed all three of their scheduled follow-up exercise tests and 33% and 25% completed two and one of their scheduled follow-up exercise tests, respectively. Given the observed effect between higher adherence and improved outcomes, it is more important to provide cardiac ER programs which can achieve increased adherence to the exercise intervention [8]. Cardiac telerehabilitation using monitoring devices and remote communication with patients has now been used more and more in the long-term management of cardiovascular diseases outside the hospital environment. Providing objective feedback data and allowing patients to track their own progress can increase patients' self-management skills and thus improve their adherence. It is convenient and can reduce anxiety, improve the quality of life and prognosis of patients with low medical costs compared with conventional ER without monitoring [9-13].
	6b	Explanation for choice of comparators page 5 Cardiac telerehabilitation using monitoring devices and remote communication with patients has now been used more and more in the long-term management of cardiovascular diseases outside

		the hospital environment. Providing objective feedback data and allowing patients to track their own progress can increase patients' self-management skills and thus improve their adherence. It is convenient and can reduce anxiety, improve the quality of life and prognosis of patients with low medical costs compared with conventional ER without monitoring [9-13].
Objectives	7	Specific objectives or hypotheses page 5 This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness and safety of home-based phase-II ER under the guidance of remote electrocardiogram （ECG）monitoring system（REMS） in the management of CHF compared with conventional ER without monitoring.
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 5 This study is a prospective, randomized, parallel controlled clinical trial to evaluate the effectiveness and safety of home-based phase-II ER under the guidance of remote electrocardiogram （ECG）monitoring system（REMS） in the management of CHF compared with conventional ER without monitoring.
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained page 6

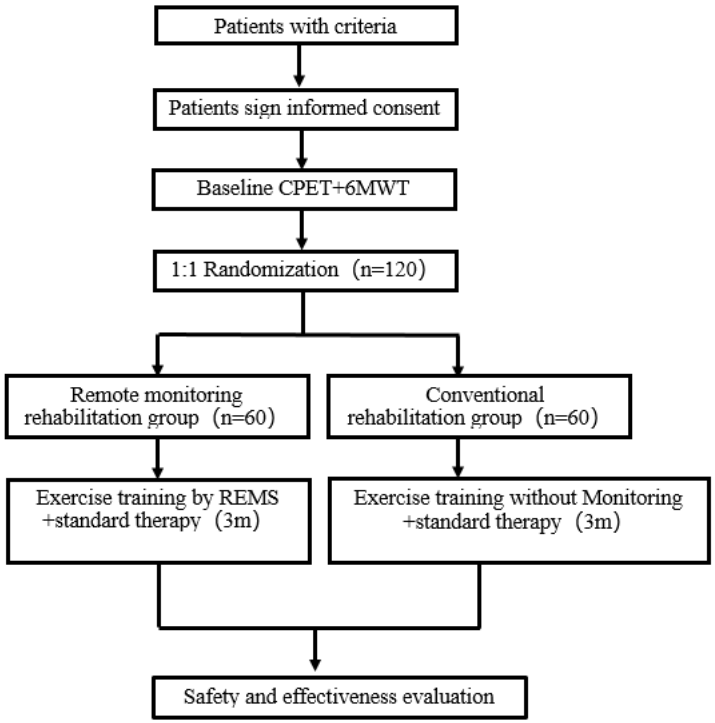
		Patients will be recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment.
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Page 6,17 Inclusion criteria: 1. Aged 18-75 years old; 2. NYHA I-III; LVEF<50% in 6 weeks before randomization; 3. in stable condition after heart failure standard drug therapy (do not need intravenous diuretics, vasoconstrictors, vasodilators or left ventricular assist device), no fluid retention, constant weight; 4. able to perform exercise rehabilitation; 5. clearly understand the content and purpose of the study and volunteer to participate in the study and sign the informed consent form. Exclusion criteria：1. exercise rehabilitation can not be carried out due to physical disability and contraindication; 2. with a contraindication to cardiopulmonary exercise test; 3. the following was happened in 3 months before admission: acute coronary syndrome, stroke, transient ischemic attack; cardiac, carotid artery or other major vascular surgery; percutaneous coronary intervention (PCI)or carotid artery angioplasty; sustained ventricular tachycardia or fibrillation; 4. coronary

		revascularization or heart transplantation is planned; 5. persistent atrial arrhythmias ; ventricular arrhythmias were not effectively controlled (using an antiarrhythmic drug or an implantable defibrillator); 6. uncorrected primary obstructive or severe regurgitant heart valve disease, restrictive or hypertrophic cardiomyopathy; 7. II or III degree heart block or sick sinus syndrome without permanent pacemaker implantation; need implantable device therapy for heart failure; 8. obstructive or bronchospasm lung disease(such as asthma, bronchitis, etc) needing oral or inhaled bronchodilator or glucocorticoids therapy; 9. pregnant or lactating women and those planning to conceive during the trial; 10. cancer or other systemic diseases with an expected survival of less than 12 months; 11. other clinical trial drugs were taken or in other medical device trial within 30 days before admission; 12. unable to participate in this study after the clinical evaluation by investigators
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered page8,9 All the patients initiate an exercise training program following the principles of exercise prescription as recommended by the American College of Sports Medicine (ACSM) and the AHA. The exercise stage order can be warm-up, main exercise, and cool-down. For the warm-up and cool-down, walking or light stretching is recommended. The main exercise is walking. Exercise training initially begins in a supervised setting and then transitions to a home-based

		regimen（Table 3 and Table 4）. The supervised training phase consists of 12 supervised training sessions, with a goal of 3 sessions per week. Patients have up to 1 month to complete the 12 sessions before transition to the home exercise phase. Patients are asked to exercise 5 times per week during the home exercise phase, totally 8 weeks. Patients begin exercising at a low intensity and then increase to a moderate intensity when they are able. The trial protocol allows patients to walk independently. In the REMS group, patients wear Inticare-MC-06 ECG monitors when exercising at home to ensure that exercise intensity is within the ranges set for them and are instructed on how to monitor their own exercise training at the beginning of the trial. During the exercise, the monitor can evaluate whether patients reach the intensity and time of the preset exercise prescription according to the heart rate. If the speed is not enough or the intensity exceeds the preset value, the system can remind the patient promptly to adjust the intensity, including speed and time course, so as to ensure the patient to exercise according to the prescription. If arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. Specialists will give an analysis report. The system will give an early warning to both patients and their doctors if the arrhythmia is risky. Doctors can check the data of their patients outside hospital, know about their conditions and give advice in time. The heart rate reserve (HRR) method is used to guide exercise intensity. Peak heart rate is derived from a patient's most recent exercise test, and the resting heart rate is taken after 5 minutes of quiet seated rest. For the first 6 supervised training sessions, the training heart rate range is

		computed at 60% of the HRR (resting heart rate + 0.6 [peak heart rate-resting heart rate]). Then training intensity is increased to 70% of the HRR for the rest of the supervised exercise training sessions. For the home-based exercise training phase, patients are asked to perform 40 minutes of aerobic exercise. In the REMS training arm, the training intensity should be maintained at 60% to 70% of the HRR. While during the whole phase of the conventional rehabilitation arm, the training intensity is not monitored.
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Page 8 If a cardiogram such as arrhythmia occurs during exercise, the system will alert the patient to stop or suspend exercise, or adjust the intensity of exercise, and upload it in real time. The data will be transformed to the data center, while specialist will give an analysis for that report. The unique algorithm can analyze the data in real time and detect suspected arrhythmias, then give the alarm and transfer data to cloud platform for doctors to check and confirm the disease. In addition, when patients have chest discomfort, palpitation and dizziness, they can mark the ECG data through One-Tap Marking button and send the data for doctors to check and give corresponding diagnosis. At the end of the monitoring, a report will be provided.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

		Page 9,10 During the training phase, participants will be asked to exercise strictly according to the prescription and record each exercise process with designed cards. Investigators will make telephone reminders before each visit and then give face-to-face reminders at each study visit emphasizing the importance of adherence. Compliance of ER in subjects are expressed in rate.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Page 9 Participants in both groups will continue standard therapy for HF. The medication should remain unchanged during the trial, while the dosage should be adjusted in case of adverse events. All procedures will be determined by physicians following the clinical guidelines.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Page 10 The primary outcome is exercise capacity improvement measured by peak oxygen uptake (VO2 peak) (baseline vs 3 m). The secondary outcomes are: (1) difference in the meters walked in the 6-min Walk Test (6MWT); (2) improvement in heart function assessed by NYHA classifications; (3) improvement in echocardiographic parameters of systolic and diastolic function; (4)changes in biomarkers, including brain natriuretic peptide（BNP）/ N-terminal-pro-brain natriuretic peptide（NT-pro-BNP）and Troponin-T/I; (5) changes in major adverse cardiovascular events (MACE) including worsening HF event, HF hospitalization, myocardial infarction, stroke, revascularization and cardiovascular mortality; (6) qualitative evaluation of patients' adherence to the rehabilitation program. The investigators will also use several validated psychometric instruments to measure health-related quality of life and depression. These measurements include

		HF Symptom Scale，Minnesota Living with Heart Failure Questionnaire (MLHFQ), 36-Item Short Form Health Survey (SF-36), Beck Depression Inventory-II (BDI-II) and General Self-Efficacy Scale (GSE).
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended Figure1 

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Page 6 The target enrollment for the trial is 120 patients. A total of 500 patients with HF (NYHA grade I-III) are treated in our hospital every year， which can be used as a screening sample. Calculated according to the lower screening rate (50%) and the designed entry criteria, the sample size that can be completed is estimated to be 100 patients. Referring to the previous foreign literature, the compliance of ER in 3 months is 70-80%. The initial screening sample size of this study is at least 120 cases, 60 cases in each group.
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Page 6 Screening will continue until the target population is achieved. A recruitment advertisement has also been utilized in our hospital.
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers) and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions Page 7 China-Japan Friendship Hospital clinical research data management platform is commissioned to

		generate a random sequence of 120 numbers using SAS 9.4 software. The random sequence will be put into sealed envelopes by staff not involved with the study to avoid selecting bias.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Page 7 After providing informed consent and undergoing baseline testing (echocardiogram and CPET), patients are randomized in a 1:1 ratio to either REMS rehabilitation group or the conventional rehabilitation group according to the time order of the patients' entry. Allocation concealment will be ensured and the randomization code will not be released until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed. Researchers involved in participants' assessments will be blinded to treatment allocation.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Page 6,7 China-Japan Friendship Hospital clinical research data management platform is commissioned to generate a random sequence of 120 numbers using SAS 9.4 software. Patients will be recruited consecutively from the outpatient service of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who will obtain written consent from patients willing to participate in the trial.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts) and how

		Page 10,11 Researchers involved in participants' assessments will be blinded to treatment allocation. All individuals involved in data management and analysis will be blinded to treatment allocation.
	17b	If blinded, circumstances under which unblinding is permissible and procedure for revealing a participant's allocated intervention during the trial N/A
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Page10,11 All patients' data will be recorded by trained clinical researchers using a standardized case report form (CRF). Original data should be recorded timely and accurately. Laboratory reports copies should also be kept. All CRFs will be stored in locked file cabinets in areas with limited access. All laboratory specimens will be identified by a coded number to maintain participant confidentiality. Data managers from Beijing Cardiar Technology, China are responsible for the data entry and management. Two data managers perform double entry independently and proofread to ensure the data accuracy. China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organizers. All individuals involved in data management and analysis will be blinded to treatment allocation. Principal investigators will have direct access to data sets. Data dispersed to project team members will be blinded of any identifying participant information.
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

		Page 9,10 During the training phase, participants will be asked to exercise strictly according to the prescription and record each exercise process with designed cards. Investigators will make telephone reminders before each visit and then give face-to-face reminders at each study visit emphasizing the importance of adherence.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Page10,11 All patients' data will be recorded by trained clinical researchers using a standardized case report form (CRF). Original data should be recorded timely and accurately. Laboratory reports copies should also be kept. All CRFs will be stored in locked file cabinets in areas with limited access. All laboratory specimens will be identified by a coded number to maintain participant confidentiality. Data managers from Beijing Cardiar Technology, China are responsible for the data entry and management. The database is established by PHP language under Linux system. Two data managers perform double entry independently and proofread to ensure the data accuracy. China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organizers. All individuals involved in data management and analysis will be blinded to treatment allocation. Principal investigators will have direct access to data sets. Data dispersed to project team members will be blinded of any identifying participant information.
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Page 11,12 Continuous variables will be presented as the mean ±standard deviation (SD), median or interquartile range (IQR). Baseline characteristics of the cohort will be summarized using

		descriptive statistics. Whether imbalances exist will be analyzed between groups. Comparison of numerical variables between the two groups is made using Student's t-test for independent samples when normally distributed. Categorical variables will be described as frequencies and percentages and compared using $\chi 2$ test. Mann-Whitney U test will be used if data are not normally distributed. Analysis of outcomes will be conducted according to the intention-to-treat (ITT) principle. We will use three analysis sets: full analysis set（FAS）, per protocol set（PPS）and safety set. The FAS includes all patients randomized, and the PPS consists of all patients who complete the treatment protocol. The safety set consists of patients who receive at least one treatment with safety records after randomization. Dropouts will be included in the analysis by modern imputation methods for missing data. All statistical tests will be 2-tailed. P<0.05 is considered statistically significant. All statistical analyses will be completed by Beijing Zhengyuan Technology Co., Ltd using SAS 9.4 software.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) page 12 Dropouts will be included in the analysis by modern imputation methods for missing data.
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Page 11,12 Analysis of outcomes will be conducted according to the intention-to-treat (ITT) principle. We will use three analysis sets: full analysis set（FAS）, per protocol set（PPS）and safety set. The FAS includes all patients randomized, and the PPS consists of all patients who complete the treatment protocol. The safety set consists of patients who receive at least one treatment with safety records after randomization.
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure;

		statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Page11 China-Japan Friendship Hospital clinical research data management platform is responsible for data monitoring, which is independent of the study organizers.
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Page 11 All adverse events that occurred during the 3-month study period will be reported in the final paper. A serious adverse event is defined as any untoward medical occurrence resulting in hospitalization or which results in a life-threatening problem, death, or disability. Adverse events will be defined as any untoward occurrences in study participants, potentially related to implementation of the study protocol. All serious and unexpected adverse events will be reported to the Ethics Committee as required.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor N/A
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

		Page 3 This study was approved by Ethics Committee of China-Japan Friendship Hospital for Clinical Research（No. 2018-55-K39）.
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) Page 5 If there is any amendment to the protocol, approval must be sought again from the Ethics Committee.
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 6 Patients will be recruited consecutively from the outpatient clinic of Cardiology Department and Integrative Cardiology Department in China-Japan Friendship Hospital by attending physicians responsible for recruitment, who will obtain written consent from patients willing to participate in the trial.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Page 11

		All CRFs will be stored in locked file cabinets in areas with limited access. All laboratory specimens will be identified by a coded number to maintain participant confidentiality.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 14 The authors declare that they have no competing interests.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Page 11 Principal investigators will have direct access to data sets. Data dispersed to project team members will be blinded of any identifying participant information.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care and for compensation to those who suffer harm from trial participation N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Page 3 The results of this study will be disseminated via peer-reviewed publications and presentations at conferences.
	31b	Authorship eligibility guidelines and any intended use of professional writers N/A Topics suggested for publication will be circulated to the principal investigators.

		No intended use of professional writers. N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code No later than 3 years after the collection of the 3m postrandomization interviews, we will deliver a deidentified data set to an appropriate data archive for sharing purposes. N/A
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates A Chinese version of informed consent (V1.1, 20180208) has been reviewed and approved by the Ethics Committee of China-Japan Friendship Hospital for Clinical Research. N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable N/A