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Complete List of Authors:	Dorje, Tashi; Curtin University - Perth City Campus, Physiotherapy and Exercise Science Zhao, Gang; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Scheer, Anna ; 1. School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia Tsokey, Lhamo ; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Wang, Jing; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Chen, Yaolin; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Tso, Khandro; 4. Internal Medicine Department, Qilian County Hospital, Qinghai, China Tan, B-K; 5. Allied Health Department, Armadale Health Service, Perth, Australia Ge, Junbo; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Shanghai, CN Maiorana, Andrew; Curtin University - Perth City Campus, School of Physiotherapy and Exercise Science
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Title: SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol

Authors: Tashi Dorje[1], Gang Zhao[2], Anna Scheer[1], Lhamo Tsokey[2], Jing Wang[2], Yaolin Chen[2], Khandro Tso[4], B-K Tan[1, 5], Junbo Ge[2], Andrew Maiorana[1, 3]

Affiliations:
1. School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia
2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China
3. Allied Health Department and Advanced Heart Failure and Cardiac Transplant Service Fiona Stanley Hospital, Perth, Australia
4. Internal Medicine Department, Qilian County Hospital, Qinghai, China
5. Allied Health Department, Armadale Health Service, Perth, Australia

Corresponding author
Associate Professor Andrew Maiorana
School of Physiotherapy Exercise Science, Curtin University, Perth, Australia
Email: A.Maiorana@curtin.edu.au
Phone number: +61 8 9266 9225
Fax number: +61 8 9266 2605

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ABSTRACT

Introduction: The burden of cardiovascular disease (CVD) is rapidly increasing in developing countries, however access to cardiac rehabilitation and secondary prevention (CR/SP) in these countries is limited. Alternative delivery models that are low-cost and easy to access are urgently needed to address this service gap. The objective of this study is to investigate whether a smartphone and social media-based (WeChat) home CR/SP program can facilitate risk factor monitoring and modification to improve disease self-management and health outcomes in patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI) therapy.

Methods and analysis: We propose a single-blind, randomised controlled trial of 300 post-PCI patients with follow-up over 12 months. The intervention group will receive a smartphone and WeChat-based CR/SP program providing education and support for risk factor monitoring and modification. SMART-CR/SP incorporates core components of modern CR/SP: physical activity tracking with interactive feedback and goal setting; education modules addressing CHD understanding and self-management; remote blood pressure monitoring and strategies to improve medication adherence. Furthermore, a dedicated data portal and a CR/SP coach will facilitate individualised supervision and counselling. The control group will receive usual care but no formal CR/SP program. The primary outcome is change in exercise capacity measured by six-minute walk test distance. Secondary outcomes include knowledge and awareness of CHD, risk factor status, medication adherence, psychological well-being and quality of life, major cardiovascular events, re-hospitalisations and all-cause mortality. To assess the feasibility and patients' acceptance of the intervention, a process evaluation will be performed at the conclusion of the study.

Ethics and dissemination: Ethics approval was granted by both the Human Research Ethics Committee of Fudan University Zhongshan Hospital [HREC B2016-058] and Curtin University Human Research Ethics Office [HRE2016-0120]. Results will be disseminated via peer-reviewed publications and presentations at conferences.

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Key words: coronary heart disease, cardiac rehabilitation, secondary prevention, social media

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STRENGTHS AND LIMITATIONS OF THE STUDY

- We propose an innovative social media-based CR/SP program to deliver community-based support for patients with CHD, after hospitalisation for PCI therapy. WeChat, a highly utilised social media application in China, will be employed to deliver a home CR/SP program to support risk factor modification and monitoring of patients with CHD. The system will enable bi-directional communication between patients and the CR/SP provider, reflecting conventional practice. To our knowledge, this will be the first study to evaluate a CR/SP program provided exclusively via social media.
- To inform the design of the intervention, end-user surveys and focus group discussions were undertaken to identify patients' needs related to CR/SP.
- This will be a single-centre study, which may limit the generalisation and application of the study results to a broader population. However, the large geographic, cultural and socioeconomic diversity of patients admitted at the study hospital may help to reduce this potential bias.
- This paper describes the rationale and protocol for a single-centre randomised controlled trial of smartphone and WeChat-based home CR/SP for patients with CHD following PCI therapy.

INTRODUCTION

The rapid economic growth and industrialisation of China over the past three decades has been paralleled by a growing epidemic of coronary heart disease (CHD). It is estimated there are over 11 million Chinese people with this disease, a figure expected to increase steadily in the next few decades.[1-3] In 2015, over 560,000 cases of percutaneous coronary intervention (PCI), a common treatment for CHD, were performed in mainland China.[1] People with established CHD are at high risk of recurrent cardiac events[4] which place a significant burden on healthcare services. However, these events can be reduced by up to half with effective secondary prevention, such as adherence to cardio-protective medication and lifestyle modification.[5]

Cardiac rehabilitation and secondary prevention (CR/SP) are systematic, evidence-based processes that facilitate the delivery of preventive therapies and improve patient outcomes after a cardiovascular event. Participation in CR/SP programs can reduce mortality by up to 25%, improve quality of life and reduce cardiovascular risk factor burden.[6-8] However, despite the well-established benefits, CR/SP services are still grossly underutilised globally. Data from developed countries, such as the United States and Australia, reported patient participation rates of between 30% and 45%, with high dropout rates of between 40% and 55%.[9-13] In low and middle income countries (LMICs), access to CR/SP services remains very low, with less than a quarter of countries having CR/SP programs.[14 15] In China, despite recent advances in the medical management of CHD, very few patients currently receive CR/SP services.[16 17] This may be due in part to the challenges associated with establishing traditional models of CR/SP in the Chinese healthcare environment, such as the lack of specific funding, staff education and training, reimbursements for participating patients.[16-18]

Accordingly, there is a need for innovative strategies to implement this evidence-based therapy in China.

Internet and smartphone-based interventions have recently been shown to be effective alternative methods for delivering rehabilitation and secondary prevention programs for people with CHD.[19-22] The rapid increase in smartphone and social media users in China has created a strong platform for the delivery of CR/SP services via these media. For example, it is reported that there are over 800 million active users of WeChat, a popular social media site in China.[23] However, there are currently no studies that have examined the feasibility and efficacy of utilising smartphones and social media to provide rehabilitation and secondary prevention services for the Chinese population. A recent study that used WeChat to support weight loss has shown positive results. In this study, participants who were more active in the WeChat-based weight loss program lost more weight, highlighting that social media may offer a promising new approach to managing chronic health conditions.[24]

It is in this context that we have developed the smartphone and WeChat-based home cardiac rehabilitation and secondary prevention (SMART-CR/SP) study.

METHODS AND ANALYSIS

Study Design

SMART-CR/SP will be a single-blind, two-arm, parallel, randomised controlled trial to evaluate the effects of CR/SP delivered via smartphone and WeChat on patient exercise capacity, knowledge and awareness of the disease, medication adherence, blood pressure, lipid profile, quality of life and clinical outcomes (Figure 1). The protocol conforms to the

SPIRIT 2013 statement and the intervention is described in accordance with the CONSORT-EHEALTH checklist.[25-27]

Eligibility and recruitment

Patients between the ages of 18-70 years with a diagnosis of CHD，including myocardial infarction, unstable or stable angina, who are treated with PCI therapy during their current admission will be eligible for inclusion. All participants will be required to personally own an operational smartphone, have an active WeChat account and sufficient Chinese language proficiency.

Exclusion criteria include: contra-indications to exercise rehabilitation (e.g. untreated ventricular tachycardia, severe heart failure, uncontrolled hypertension or hypotension, significant exercise limitations), an inability to operate a smartphone for the purpose of the trial (e.g. vision, hearing, cognitive or dexterity impairment), lack of internet access at place of residence, or having pre-existing comorbid disease with a life expectancy of less than one year.

Recruitment will occur during hospital admission at Fudan University Zhongshan Hospital in Shanghai. The hospital is a preeminent public hospital in Eastern China, servicing a culturally and socioeconomically diverse population from across the nation. Patients admitted with CHD, and who receive PCI therapy during their admission, will be screened and those meeting the inclusion criteria will be invited to participate in the study. A face-to-face interview will be arranged for patients who express an interest in the trial, and formal written consent will be obtained from candidates who agree to participate.

Sample size calculation

A 25 metre improvement in the six-minute walk test (6MWT) is considered to be clinically meaningful.[28-30] Thus, to detect a minimal clinically important difference of 25 meters for the 6MWT with 90% power (type I error = 5%, two-sided test), we will require a total sample size of 242 across both arms of the study. Assuming, an estimated 20% loss to follow-up, we plan to recruit a total of 300 participants.

Ethics approval

Primary ethics approval for this trial was granted by the Human Research Ethics Committee of Fudan University Zhongshan Hospital [HREC B2016-058]. The Curtin University Human Research Ethics Office granted the reciprocal approval for the trial [HRE2016-0120].

Randomisation and blinding

Following provision of consent, participants will be randomised in a 1:1 fashion to a smartphone and WeChat-based cardiac rehabilitation and secondary prevention program (SMART-CR/SP) group, or a usual care group by using the random allocation sequences generated from SAS software (SAS Institute Inc., Cary, NC, USA). The SMART-CR/SP program will be initiated within two weeks of participant discharge following PCI therapy. Participants will be informed of their group allocation through a single WeChat message. Additionally, participants in the intervention group will receive their first cartoon-format WeChat article, illustrating the SMART-CR/SP program, to familiarise them with the system and mobile technologies involved. Additional technology training will be provided if required by the participant. Research personnel involved in participants' assessments be blinded to treatment allocation.

Control (usual care) group

Participants in the usual care group will receive standard care as provided by their community doctors and cardiologists after hospital discharge. In China, current post-PCI care involves brief inpatient health education provided by a ward nurse, medication management and ad hoc follow-up visits to a cardiologist or other health care providers according to the patient's self -assessment of their own cardiovascular health.

Intervention group

In addition to usual care, participants in the SMART-CR/SP group will receive an eight week comprehensive smartphone and WeChat-based home CR/SP program providing core components of guideline advocated CR/SP for post-PCI CHD patients,[31 32] followed by a 16-week 'step-down' program. Figure 2 provides a pictorial representation of the interactive system.

Cardiac health education

A culturally appropriate and user-friendly WeChat-based cardiac health education system has been developed for this trial, which consists of 32 episodes of cartoon-format CHD educational articles, covering a broad range of cardiovascular health education topics relevant to post-PCI CHD patients (Figure 3). In the first eight weeks, participants will receive four WeChat educational articles per week. Each of the articles will introduce one key educational topic using a short interactive story involving dialogue between a patient and cardiologist avatar that is illustrated by 20-30 cartoon drawing slides. In the 'step-down' program, two cartoon drawing slides with a key motivational message attached to each will be sent to participants' WeChat account every week. The WeChat articles/slides and messages will be sent during random working hours on random weekdays from an official WeChat account (avatar name: Dr. Kang: an abbreviation of "rehabilitation" in Chinese). Table 1 shows the content of the cardiac health education.

Role of the CR/SP coach

A cardiologist will act as the CR/SP coach, whose main task is to review participants' data on a regular basis and provide guidance and medical advice as required. All questions and enquiries from participants will be reviewed and replied to by the CR/SP coach using the study's official WeChat account (Dr Kang). Replies will be made within one business day, and video calls will be booked if required by the participants.

Exercise prescription and physical activity tracking

Participants will receive an individualised walking program based on their baseline 6MWT, with both the time and intensity of walking increased gradually over the first eight weeks. The target physical activity level will be 10,000 accumulated steps of walking per day, at least five times per week, in accordance with international recommendations.[33] Utilising WeChat's physical activity tracker, WeChat Sports, participants will be able to review their real-time, weekly and monthly step counts. The CR/SP coach, as a WeChat 'friend' of the participant, will have access to their step counts and will review participants' physical activity data on a weekly basis, provide guidance and positive reinforcement on days that target physical activity levels are achieved. Participants will also be encouraged to undertake other forms of physical activity, such as swimming, Tai Chi, group dancing and table tennis.

Blood pressure monitoring and management

Participants will be provided with a Bluetooth enabled blood pressure monitoring device (C-health XY-10, Sky Innovation Technology Ltd. (Shanghai)), and will be asked to measure their blood pressure on two days per week, with two measurements each day, one minute apart. The blood pressure readings will be transmitted via Bluetooth technology to a dedicated application on participants' smartphones where it will be uploaded to a data

management portal which will be reviewed by the CR/SP and appropriate guidance will be provided to participants according to contemporary guidelines.[34] A standard procedure and alerts will be employed when participant's measurement readings are outside the target levels. This will include WeChat alert messages send by the CR/SP coach to remind participants for repeat blood pressure measurements, medication adherence and to seek medical advice from their health care givers if indicated. WeChat-based counselling will be provided if participant prefers to receive advice from the CR/SP coach. This alert system will be ceased once the target blood pressure is achieved. To facilitate the ability of both the participants and the CR/SP coach to review the blood pressure data, blood pressure management applications will be installed on both participants' and physician's smartphone.

Cardiovascular risk factor monitoring and management

Cardiovascular risk factors for each participant will be assessed during the baseline face-to-face assessment. This will involve a detailed review of the participant's PCI therapy, blood pressure, family history of CVD, glucose levels, lipid profile, smoking status, body mass index (BMI), hip and waist circumferences, dietary habit, existing sleep apnoea, and diabetes. Data will be collected and managed using the REDCap electronic data capture tool hosted at Fudan University.[35] After the initial assessment, participants will be informed of their target level for each risk factor by the CR/SP coach, and encouraged to try and achieve this goal. Participants can update their CVD risk factor profile at any time through communication with the CR/SP coach on WeChat.

Healthy nutrition

To help participants understand and comply with dietary recommendations, cartoon-format educational articles developed according to contemporary guidelines[36-38] will be sent to their WeChat account. Cultural considerations have been taken into account when developing the

dietary content of the educational articles. In addition, participants will be able to photograph the food they consume and send the pictures to the CR-SP coach through WeChat to get feedback on the nutritional content of the food.

Cardiac medication management

The medication list of each participant will be reviewed by the CR/SP coach at baseline to ensure that the five classes of recommended cardio-protective medications have been prescribed (aspirin, adenosine diphosphate (ADP) receptor antagonist, beta-blocker, angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blockers (ARBs), and a statin/ lipid-lowering medication). If any of the cardio-protective medications are not prescribed for the participant then underlying reasons (contraindicated/previously documented intolerance) will be investigated. The participant will be notified and encouraged by the CR/SP coach to discuss their medication therapy with their doctors if they are not prescribed with these medications without justification. Additionally, information relating to the mechanism of these drugs, evidence of clinical benefits, and common side effects will be described in detail in the WeChat cartoon-format educational articles to increase understanding and compliance rates.

Outcome assessment

The outcome measures for the trial are outlined in Table 2. Baseline assessments will occur within two weeks of participants' discharge from hospital, with follow up at eight weeks, six months and 12 months to evaluate both the short-term and longer-term efficacy of the CR/SP intervention. The primary outcome will be the change in exercise capacity from baseline, as assessed by 6MWT distance at eight weeks and six months, using a standardised protocol.[39] In the 6MWT, oxygen saturation, blood pressure, and heart rate of participants will be measured pre- and post-test.

Secondary outcomes will be participant knowledge of CHD, evaluated by a CHD knowledge questionnaire based on two validated heart disease questionnaires,[40 41] resting blood pressure, fasting plasma glucose and cholesterol levels, adherence to cardio-protective medications, behavioural CHD risk factors including unhealthy diet (WHO Steps instrument);[42] smoking (Fagerström Test for Nicotine Dependence);[43] low physical activity (IPAQ), overweight or obesity, as well as psychosocial factors including anxiety symptoms (Generalized Anxiety Disorder 7-item scale), depressive symptoms (SF-12 V2™ Health Survey), major cardiovascular events (MACE), and all-cause mortality.

Health system and associated resource use relating to CHD will be collected during each follow up visit from participants' self-report and cross-checked against hospital records. This will include: emergency department presentations, hospital admissions, outpatient clinic attendances, and community doctor and specialist consultations. The cost of resource use relating to CHD will be valued based on the current manual of resource items and their associated costs published by the Shanghai Municipal Health and Family Planning Commission.

Evaluation of participants' perceptions of SMART CR/SP

Process evaluation will be undertaken by user surveys and focus group discussions. At the completion of the trial, participants from the intervention group will be invited to complete a WeChat-based questionnaire to evaluate their experience and perceptions of the program. A sub-group of participants from the intervention group will be randomly selected and invited to participate in focus group discussions, to gain a more in-depth understanding of the end-users' acceptability of the program, their experiences, and expectations of future smartphone and social media-based CR/SP models. We anticipate approximately five focus groups will be required, however, sampling will be ceased once thematic saturation is reached. Focus groups will be conducted by an experienced researcher (Dr Gang Zhao), digitally recorded

and transcribed. Data will be sorted, coded and assigned to categories based on the objectives via an inductive approach.

Statistical considerations

The intention to treat principle will be adopted and participants' outcomes will be analysed according to the group to which they are allocated. Baseline characteristics of the cohort will be summarised using descriptive statistics. Continuous variables will be reported as mean and standard deviation and be compared using student's *t* test. Categorical variables will be described as frequencies and percentages and compared using Chi-square test. Mann-whitney U test will be used if data are not normally distributed. A Cox proportional hazard model will be performed to analyse hospital readmission, outpatient clinic and emergency department visits. The criterion for statistical significance will be set at $P<0.05$. The statistical analysis will be conducted using SPSSv24 (IBM, USA).

DISCUSSION

The SMART-CR/SP study will evaluate the feasibility and impact of an innovative smartphone and WeChat-based home CR/SP program for patients with CHD after PCI therapy. We are not aware of any previously published studies that have reported the efficacy of a smartphone and social media CR/SP service delivery model.

Cardiac rehabilitation and secondary prevention is a Class I recommendation for the management of CHD patients.[31] However, despite the growing evidence of its cost-effectiveness[11] and efficacy in reducing cardiovascular morbidity and mortality,[8] CR/SP services are limited in China. A recent national survey showed that only 30 of 124 (24%) large medical centres surveyed in China have operational CR programs, translating to

approximately two programs per 100 million inhabitants.[16] To address this service provision gap, there is a clear need to develop alternative delivery models to increase access to CR/SP services. Social media offers great potential for delivering health education and support through smartphones. Compared with past telephone and text message support, smartphones and social media may provide a more powerful, multi-functional platform for disease management. This includes access to step counting, multi-media messaging, voice/video call and group discussion. In China, and other LMICs, where access to tertiary and secondary prevention health care are often limited, these advanced technology functions may greatly facilitate the delivery of core components of modern CR/SP to many CHD patients who would not otherwise have had access to these important services. The potential reach of a smartphone and social media-based CR/SP intervention is great as it could easily be expanded to reach many smartphone and social media users at a low cost. Furthermore, this innovative service model could overcome common barriers to patients participating CR/SP program, such as inconvenience, geographical isolation and financial burden, [21 22 24] given it is easy to access, flexibility and low cost.

In conclusion, SMART-CR/SP will test the utility of a smartphone and WeChat-based intervention to deliver the core components of guideline advocated CR/SP. If the efficacy of this social media-based CR/SP intervention is validated, this will have significant potential to improve access to evidence-based CR/SP for patients with CHD. This is likely to translate to improved patient outcomes and reduced financial burden of CVD on health systems. Although the focus of this study is the delivery of a CR/SP intervention via smartphone and WeChat, there is great potential that this model of care could be adopted in both the primary and secondary prevention context for other chronic diseases, and using other social media platforms.

COMPETING INTERESTS

We declare that there are no conflicts of interest related to this clinical trial.

CONSENT FOR PUBLICATION

The manuscript does not contain any individual patient's data in any form.

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AUTHOR'S CONTRIBUTIONS

TD and AM conceived the original concept of the study and wrote the first draft of the protocol manuscript. ZG, AS, LT, JW, YLC, KT, BKT, JBG contributed to the design of the study. All authors read and approved the final manuscript.

ETHICS AND DISSEMINATION

The Human Research Ethics Committee of Fudan University Zhongshan Hospital granted the primary ethics approval for the trial [HREC B2016-058]. The Curtin University Human Research Ethics Office granted the reciprocal approval for the trial [HRE2016-0120]. The report of the study will be disseminated via the usual scientific forums including peer-reviewed publications and presentations at national and international conferences.

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Table 1. Topic list of WeChat-based cartoon-format health education

1.	Welcome to SMART-CR/SP from Dr Kang
2.	Mr. Li's heart attack (episode 1)
3.	Mr. Li's heart attack (episode 2)
4.	How you heart works
5.	Coronary heart disease
6.	Angina and management
7.	Heart attack signs
8.	Action plan for heart attack
9.	Risk factors of coronary heart disease
10.	Clinical tests for coronary heart disease
11.	Percutaneous coronary intervention therapy
12.	Medication management after percutaneous intervention therapy
13.	Physical activity after percutaneous intervention therapy (episode 1)
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15.	Physical activity after percutaneous intervention therapy (episode 3)
16.	Healthy eating (episode 1)
17.	Healthy eating (episode 2)
18.	Healthy eating (episode 3)
19.	Diet-fat facts
20.	Diet-salt facts
21.	Smoking cessation
22.	Blood pressure management
23.	Management of cholesterol
24.	Management of diabetes
25.	Weight management
26.	Alcohol and heart health
27.	Mental health and heart health
28.	Back to normal life after percutaneous coronary intervention
29.	Myths about coronary heart disease
30.	Cardiac pulmonary resuscitation

31.	Hands-only cardiac pulmonary resuscitation
32.	Goodbye and long-term management

Table 2. Assessment time-points for primary and secondary outcomes of SMART-CR/SP

Outcome	Assessment	Baseline	8-week	6-month	12-month
Primary outcome					
Exercise capacity	Change in 6MWT distance	✓	✓	✓	
Key secondary outcome					
Knowledge of the disease	Modified CHD questionnaire[40 41]	✓	✓	✓	✓
Secondary outcomes					
Blood pressure	Average of two resting, sitting digital recordings	✓	✓	✓	
Lipid profile	Fasting blood sample	✓	✓	✓	✓
Medication adherence	Adherent to cardiac-protective medications	✓	✓	✓	✓
Smoking	Self-report	✓	✓	✓	✓
Obesity	Weight, height, waist and hip circumference	✓	✓	✓	
Physical activity	General Physical Activity Questionnaire[44]	✓	✓	✓	✓
Fruit and vegetable intake	WHO Steps instrument[42]	✓	✓	✓	✓
Anxiety symptoms	Generalized Anxiety Disorder 7-item (GAD-7) scale[45]	✓	✓	✓	✓
Depressive symptoms	Patient Health Questionnaire (PHQ-9)[46]	✓	✓	✓	✓
Quality of life	SF-12_V2™ Health Survey[47]	✓	✓	✓	✓
CV events	CVD death, non-fatal AMI, stroke or hospital admission with unstable angina or congestive heart failure		✓	✓	✓
CR/SP needs survey	Patient needs for the core components of CR/SP [31]	✓	✓	✓	✓
All-cause mortality	Data from CDC		✓	✓	✓

6MWT, six minute walk test distance; CHD, coronary heart disease; CR/SP, cardiac rehabilitation and secondary prevention; AMI, acute myocardial infarction; BP, blood pressure; CV, cardiovascular; LDL, low-density lipoprotein; WHO, World Health Organization; CDC, Centre Disease Control and Prevention.

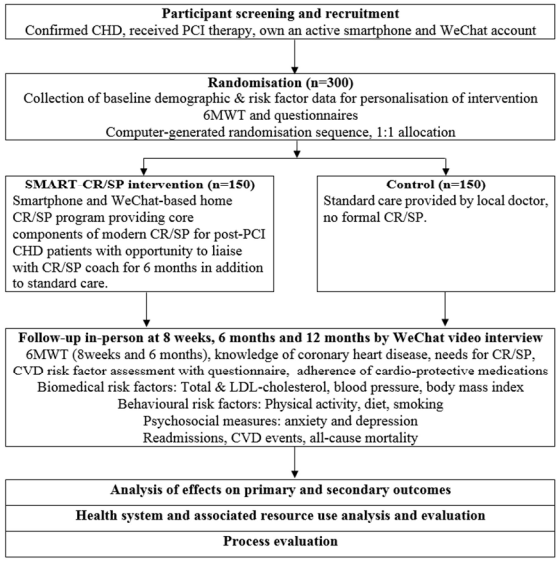

Figure 1. Randomised controlled trial design and flowchart. The control group will receive usual care but no formal CR/SP. The intervention group will receive a smartphone and WeChat-based CR/SP program providing education and support for risk factor monitoring and modification.

338x190mm (300 x 300 DPI)

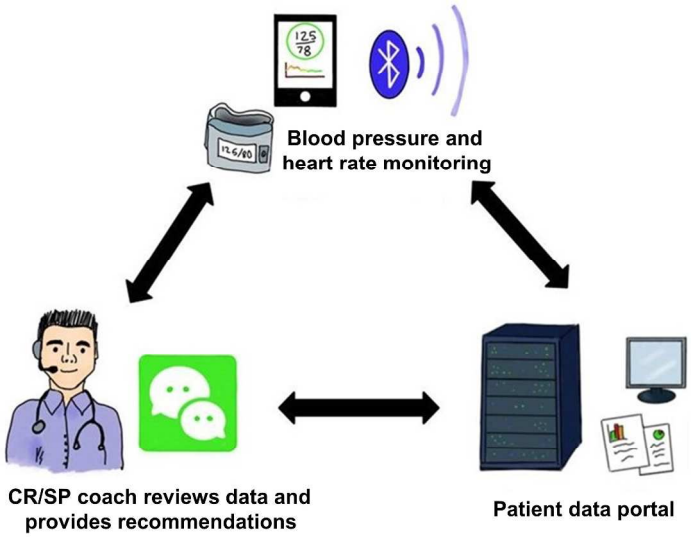

Figure 2. Components of the SMART-CR/SP system: physical activity tracking with interactive feedback and goal setting; education modules addressing disease understanding and self-management; remote blood pressure monitoring and strategies to improve medication adherence. Furthermore, a dedicated data portal and a CR/SP coach will facilitate individualised supervision and counselling.

338x190mm (300 x 300 DPI)

Figure 3. SMART-CR/SP system interface depicting health education(a), physical activity tracking(b), blood pressure monitoring(c), cholesterol management(d), medication management(e), individual counselling(f), smoking secession(g), mental health(h)‼ ┼ ‼ ┼

338x190mm (300 x 300 DPI)

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SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol

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Complete List of Authors:	Dorje, Tashi; Curtin University - Perth City Campus, Physiotherapy and Exercise Science Zhao, Gang; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Scheer, Anna ; 1. School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia Tsokey, Lhamo ; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Wang, Jing; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Chen, Yaolin; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Tso, Khandro; 4. Internal Medicine Department, Qilian County Hospital, Qinghai, China Tan, B-K; 5. Allied Health Department, Armadale Health Service, Perth, Australia Ge, Junbo; 2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China Shanghai, CN Maiorana, Andrew; Curtin University - Perth City Campus, School of Physiotherapy and Exercise Science
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Coronary heart disease < CARDIOLOGY, cardiac rehabilitation, secondary prevention, social media, WeChat

Title: SMARTphone and social media-based Cardiac Rehabilitation and Secondary Prevention (SMART-CR/SP) for patients with coronary heart disease in China: a randomised controlled trial protocol

Authors: Tashi Dorje[1], Gang Zhao[2], Anna Scheer[1], Lhamo Tsokey[2], Jing Wang[2], Yaolin Chen[2], Khandro Tso[4], B-K Tan[1, 5], Junbo Ge[2], Andrew Maiorana[1, 3]

Affiliations:
1. School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia
2. Department of Cardiology, Fudan University Zhongshan Hospital, Shanghai, China
3. Allied Health Department and Advanced Heart Failure and Cardiac Transplant Service Fiona Stanley Hospital, Perth, Australia
4. Internal Medicine Department, Qilian County Hospital, Qinghai, China
5. Allied Health Department, Armadale Health Service, Perth, Australia

Corresponding author
Associate Professor Andrew Maiorana
School of Physiotherapy and Exercise Science, Curtin University, Perth, Australia
Email: A.Maiorana@curtin.edu.au
Phone number: +61 8 9266 9225
Fax number: +61 8 9266 2605

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ABSTRACT

Introduction: The burden of cardiovascular disease (CVD) is rapidly increasing in developing countries, however access to cardiac rehabilitation and secondary prevention (CR/SP) in these countries is limited. Alternative delivery models that are low-cost and easy to access are urgently needed to address this service gap. The objective of this study is to investigate whether a smartphone and social media-based (WeChat) home CR/SP program can facilitate risk factor monitoring and modification to improve disease self-management and health outcomes in patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI) therapy.

Methods and analysis: We propose a single-blind, randomised controlled trial of 300 post-PCI patients with follow-up over 12 months. The intervention group will receive a smartphone-based and WeChat-based CR/SP program providing education and support for risk factor monitoring and modification. SMART-CR/SP incorporates core components of modern CR/SP: physical activity tracking with interactive feedback and goal setting; education modules addressing CHD understanding and self-management; remote blood pressure monitoring and strategies to improve medication adherence. Furthermore, a dedicated data portal and a CR/SP coach will facilitate individualised supervision and counselling. The control group will receive usual care but no formal CR/SP program. The primary outcome is change in exercise capacity measured by six-minute walk test distance. Secondary outcomes include knowledge and awareness of CHD, risk factor status, medication adherence, psychological well-being and quality of life, major cardiovascular events, re-hospitalisations and all-cause mortality. To assess the feasibility and patients' acceptance of the intervention, a process evaluation will be performed at the conclusion of the study.

Ethics and dissemination: Ethics approval was granted by both the Human Research Ethics Committee of Fudan University Zhongshan Hospital [HREC B2016-058] and Curtin University Human Research Ethics Office [HRE2016-0120]. Results will be disseminated via peer-reviewed publications and presentations at conferences.

Clinical Trials registration number ChiCTR-INR-16009598

Key words: coronary heart disease, cardiac rehabilitation, secondary prevention, social media

Word count: 308

STRENGTHS AND LIMITATIONS OF THE STUDY

- We propose an innovative social media-based cardiac rehabilitation/secondary prevention (CR/SP) program to deliver community-based support for patients with coronary heart disease, after hospitalisation for percutaneous coronary intervention therapy. To our knowledge, this will be the first study to evaluate a CR/SP program provided exclusively via social media.
- To inform the design of the intervention, end-user surveys and focus group discussions were undertaken to identify patients' needs related to CR/SP.
- This will be a single-centre study, which may limit the generalisation and application of the study results to a broader population. However, the large geographic, cultural and socioeconomic diversity of patients admitted at the study hospital may help to reduce this potential bias.
- The study is limited to patients with smartphones and internet access.
- It is possible that the increased exposure to the health system experienced by participants in the experimental group will influence their behaviour, independent of the effects of the mHealth intervention.

INTRODUCTION

The rapid economic growth and industrialisation of China over the past three decades has been paralleled by a growing epidemic of coronary heart disease (CHD). It is estimated there are over 11 million Chinese people with this disease, a figure expected to increase steadily in the next few decades.[1-3] In 2015, over 560,000 cases of percutaneous coronary intervention (PCI), a common treatment for CHD, were performed in mainland China.[1] People with established CHD are at high risk of recurrent cardiac events[4] which place a significant burden on healthcare services. However, these events can be reduced by up to half with effective secondary prevention, such as adherence to cardio-protective medication and lifestyle modification.[5]

Cardiac rehabilitation and secondary prevention (CR/SP) are systematic, evidence-based processes that facilitate the delivery of preventive therapies and improve patient outcomes after a cardiovascular event. Participation in CR/SP programs can reduce mortality by up to 25%, improve quality of life and reduce cardiovascular risk factor burden.[6 7] However, despite the well-established benefits, CR/SP services are still grossly underutilised globally. Data from developed countries, such as the United States and Australia, reported patient participation rates of between 30% and 45%, with high dropout rates of between 40% and 55%.[8-12] In low and middle income countries (LMICs), access to CR/SP services remains very low, with less than a quarter of countries having CR/SP programs.[13 14] In China, despite recent advances in the medical management of CHD, very few patients currently receive CR/SP services.[15 16] This may be due in part to the challenges associated with establishing traditional models of CR/SP in the Chinese healthcare environment, such as the lack of specific funding, staff education and training, reimbursements for participating patients.[15-17]

Accordingly, there is a need for innovative strategies to implement this evidence-based therapy in China.

Internet and smartphone-based interventions have recently been shown to be effective alternative methods for delivering rehabilitation and secondary prevention programs for people with CHD.[18-21] Especially in the context of risk factor modification and behaviour change[22-24]. The rapid increase in smartphone and social media users in China has created a strong platform for the delivery of CR/SP services via these media. For example, it is reported that there are over 800 million active users of WeChat, a popular social media site in China.[25] However, there are currently no studies that have examined the feasibility and efficacy of utilising smartphones and social media to provide rehabilitation and secondary prevention services for the Chinese population. A recent study that used WeChat to support weight loss has shown positive results. In this study, participants who were more active in the WeChat-based weight loss program lost more weight, highlighting that social media may offer a promising new approach to managing chronic health conditions.[26]

It is in this context that we have developed the smartphone and WeChat-based home cardiac rehabilitation and secondary prevention (SMART-CR/SP) study.

METHODS AND ANALYSIS

Study Design

SMART-CR/SP will be a single-blind, two-arm, parallel, randomised controlled trial to evaluate the effects of CR/SP delivered via smartphone and WeChat on patient exercise capacity, knowledge and awareness of the disease, medication adherence, blood pressure, lipid profile, quality of life and clinical outcomes (Figure 1). The protocol conforms to the

SPIRIT 2013 statement and the intervention is described in accordance with the CONSORT-EHEALTH checklist.[27-29]

Eligibility and recruitment

Patients between the ages of 18-70 years with a diagnosis of CHD，including myocardial infarction, unstable or stable angina, who are treated with PCI therapy during their current admission will be eligible for inclusion. All participants will be required to personally own an operational smartphone, have an active WeChat account and sufficient Chinese language proficiency.

Exclusion criteria include: contra-indications to exercise rehabilitation (e.g. untreated ventricular tachycardia, severe heart failure, uncontrolled hypertension or hypotension, significant exercise limitations), an inability to operate a smartphone for the purpose of the trial (e.g. vision, hearing, cognitive or dexterity impairment), lack of internet access at place of residence, or having pre-existing comorbid disease with a life expectancy of less than one year.

Recruitment will occur during hospital admission at Fudan University Zhongshan Hospital in Shanghai. The hospital is a preeminent public hospital in Eastern China, servicing a culturally and socioeconomically diverse population from across the nation. Patients admitted with CHD, and who receive PCI therapy during their admission, will be screened and those meeting the inclusion criteria will be invited to participate in the study. A face-to-face interview will be arranged for patients who express an interest in the trial, and formal written consent will be obtained from candidates who agree to participate.

Sample size calculation

A 25 metre improvement in the six-minute walk test (6MWT) is considered to be clinically meaningful.[30-32] Thus, to detect a minimal clinically important difference of 25 meters for the 6MWT with 90% power (type I error = 5%, two-sided test), assuming a SD of 60 meters[18], we will require a total sample size of 242 across both arms of the study. Assuming, an estimated 20% loss to follow-up, we plan to recruit a total of 300 participants.

Randomisation and blinding

Following provision of consent, participants will be randomised in a 1:1 fashion to a smartphone and WeChat-based cardiac rehabilitation and secondary prevention program (SMART-CR/SP) group, or a usual care group by using the random allocation sequences generated from SAS software (SAS Institute Inc., Cary, NC, USA). The SMART-CR/SP program will be initiated within two weeks of participant discharge following PCI therapy. Participants will be informed of their group allocation through a single WeChat message. Additionally, participants in the intervention group will receive their first cartoon-format WeChat article, illustrating the SMART-CR/SP program, to familiarise them with the system and mobile technologies involved. Additional technology training will be provided if required by the participant. Research personnel involved in participants' assessments will be blinded to treatment allocation.

Control (usual care) group

Participants in the usual care group will receive standard care as provided by their community doctors and cardiologists after hospital discharge. In China, current post-PCI care involves brief inpatient health education provided by a ward nurse, medication management and ad hoc follow-up visits to a cardiologist or other health care providers according to the patient's self -assessment of their own cardiovascular health.

Intervention group

In addition to usual care, participants in the SMART-CR/SP group will receive an eight week comprehensive smartphone and WeChat-based home CR/SP program providing core components of guideline advocated CR/SP for post-PCI CHD patients,[33 34] followed by a 16-week 'step-down' program. Figure 2 provides a pictorial representation of the interactive system.

Cardiac health education

A culturally appropriate and user-friendly WeChat-based cardiac health education system has been developed for this trial, which consists of 32 episodes of cartoon-format CHD educational articles, covering a broad range of cardiovascular health education topics relevant to post-PCI CHD patients (Figure 3). In the first eight weeks, participants will receive four WeChat educational articles per week. Each of the articles will introduce one key educational topic using a short interactive story involving dialogue between a patient and cardiologist avatar that is illustrated by 20-30 cartoon drawing slides. In the 'step-down' program, two cartoon drawing slides with a key motivational message attached to each will be sent to participants' WeChat account every week. The WeChat articles/slides and messages will be sent during random working hours on random weekdays from an official WeChat account (avatar name: Dr. Kang: an abbreviation of "rehabilitation" in Chinese). Table 1 shows the content of the cardiac health education.

Role of the CR/SP coach

A cardiologist will act as the CR/SP coach, whose main task is to review participants' data on a regular basis and provide guidance and medical advice as required. All questions and enquiries from participants will be reviewed and replied to by the CR/SP coach using the

study's official WeChat account (Dr Kang). Replies will be made within one business day, and video calls will be booked if required by the participants.

Exercise prescription and physical activity tracking

Participants will receive an individualised walking program based on their baseline 6MWT, with both the time and intensity of walking increased gradually over the first eight weeks. The target physical activity level will be 10,000 accumulated steps of walking per day, at least five times per week, in accordance with international recommendations.[35] Utilising WeChat's physical activity tracker, WeChat Sports, participants will be able to review their real-time, weekly and monthly step counts. The CR/SP coach, as a WeChat 'friend' of the participant, will have access to their step counts and will review participants' physical activity data on a weekly basis, provide guidance and positive reinforcement on days that target physical activity levels are achieved. Participants will also be encouraged to undertake other forms of physical activity, such as swimming, Tai Chi, group dancing and table tennis.

Blood pressure monitoring and management

Participants will be provided with a Bluetooth enabled blood pressure monitoring device (C-health XY-10, Sky Innovation Technology Ltd. (Shanghai)), and will be asked to measure their blood pressure on two days per week, with two measurements each day, one minute apart. The blood pressure readings will be transmitted via Bluetooth technology to a dedicated application on participants' smartphones where it will be uploaded to a data management portal which will be reviewed by the CR/SP and appropriate guidance will be provided to participants according to contemporary guidelines.[36] A standard procedure and alerts will be employed when participant's measurement readings are outside the target levels.

This will include WeChat alert messages send by the CR/SP coach to remind participants for repeat blood pressure measurements, medication adherence and to seek medical advice from their health care givers if indicated. WeChat-based counselling will be provided if participant prefers to receive advice from the CR/SP coach. This alert system will be ceased once the target blood pressure is achieved. To facilitate the ability of both the participants and the CR/SP coach to review the blood pressure data, blood pressure management applications will be installed on both participants' and physician's smartphone.

Cardiovascular risk factor monitoring and management

Cardiovascular risk factors for each participant will be assessed during the baseline face-to-face assessment. This will involve a detailed review of the participant's PCI therapy, blood pressure, family history of CVD, glucose levels, lipid profile, smoking status, body mass index (BMI), hip and waist circumferences, dietary habit, existing sleep apnoea, and diabetes. Data will be collected and managed using the REDCap electronic data capture tool hosted at Fudan University.[37] After the initial assessment, participants will be informed of their target level for each risk factor by the CR/SP coach, and encouraged to try and achieve this goal. Participants can update their CVD risk factor profile at any time through communication with the CR/SP coach on WeChat.

Healthy nutrition

To help participants understand and comply with dietary recommendations, cartoon-format educational articles developed according to contemporary guidelines[38-40] will be sent to their WeChat account. Cultural considerations have been taken into account when developing the dietary content of the educational articles. In addition, participants will be able to photograph the food they consume and send the pictures to the CR-SP coach through WeChat to get feedback on the nutritional content of the food.

Cardiac medication management

The medication list of each participant will be reviewed by the CR/SP coach at baseline to ensure that the five classes of recommended cardio-protective medications have been prescribed (aspirin, adenosine diphosphate (ADP) receptor antagonist, beta-blocker, angiotensin-converting-enzyme (ACE) inhibitor or angiotensin II receptor blockers (ARBs), and a statin/ lipid-lowering medication). If any of the cardio-protective medications are not prescribed for the participant then underlying reasons (contraindicated/previously documented intolerance) will be investigated. The participant will be notified and encouraged by the CR/SP coach to discuss their medication therapy with their doctors if they are not prescribed with these medications without justification. Additionally, information relating to the mechanism of these drugs, evidence of clinical benefits, and common side effects will be described in detail in the WeChat cartoon-format educational articles to increase understanding and compliance rates.

Outcome assessment

The outcome measures for the trial are outlined in Table 2. Baseline assessments will occur within two weeks of participants' discharge from hospital, with follow up at eight weeks, six months and 12 months to evaluate both the short-term and longer-term efficacy of the CR/SP intervention. The primary outcome will be the change in exercise capacity from baseline, as assessed by 6MWT distance at eight weeks and six months, using a standardised protocol.[41] In the 6MWT, oxygen saturation, blood pressure, and heart rate of participants will be measured pre- and post-test.

Secondary outcomes will be participant knowledge of CHD, evaluated by a CHD knowledge questionnaire based on two validated heart disease questionnaires,[42 43] resting blood pressure, fasting plasma glucose and cholesterol levels, adherence to cardio-protective medications,

behavioural CHD risk factors including unhealthy diet (WHO Steps instrument);[44] smoking (Fagerström Test for Nicotine Dependence);[45] low physical activity (IPAQ),[46] overweight or obesity, as well as psychosocial factors including anxiety symptoms (Generalized Anxiety Disorder 7-item scale),[47] depressive symptoms (Patient Health Questionnaire),[48] quality of life (SF-12 V2™ Health Survey),[49] major cardiovascular events (MACE), and all-cause mortality.

Health system and associated resource use relating to CHD will be collected during each follow up visit from participants' self-report and cross-checked against hospital records. This will include: emergency department presentations, hospital admissions, outpatient clinic attendances, and community doctor and specialist consultations. The cost of resource use relating to CHD will be valued based on the current manual of resource items and their associated costs published by the Shanghai Municipal Health and Family Planning Commission.

Evaluation of participants' perceptions of SMART CR/SP

Process evaluation will be undertaken by user surveys and focus group discussions. At the completion of the trial, participants from the intervention group will be invited to complete a WeChat-based questionnaire to evaluate their experience and perceptions of the program. A sub-group of participants from the intervention group will be randomly selected and invited to participate in focus group discussions, to gain a more in-depth understanding of the end-users' acceptability of the program, their experiences, and expectations of future smartphone and social media-based CR/SP models. We anticipate approximately five focus groups will be required, however, sampling will be ceased once thematic saturation is reached. Focus groups will be conducted by an experienced researcher (Dr Gang Zhao), digitally recorded and transcribed. Data will be sorted, coded and assigned to categories based on the objectives via an inductive approach.

Statistical considerations and data management

The intention to treat principle will be adopted and participants' outcomes will be analysed according to the group to which they are allocated. Baseline characteristics of the cohort will be summarised using descriptive statistics. Continuous variables will be reported as mean and standard deviation and be compared using linear regression models. Potential confounders and baseline values of the dependent variables will be entered as covariates. Categorical variables will be described as frequencies and percentages and compared using Chi-square test. Mann-whitney U test will be used if data are not normally distributed. A Cox proportional hazard model will be performed to analyse hospital readmission, outpatient clinic and emergency department visits. The criterion for statistical significance will be set at $P<0.05$. The statistical analysis will be conducted using SPSSv24 (IBM, USA).

Data will be de-identified once collected, and a study ID will be developed for each participant. Only authorized researchers will have access to the data. Furthermore, a variety of security controls will be implemented. Given the short period of the intervention and low risk of the trial, a data monitoring committee will not be formed. However, regular data review will be performed to minimize adverse events and other unintended effects.

Patient and public involvement

Patient and public involvement (PPI) played a key role in this study. During the study design, intervention platform development and piloting, post PCI patients and their relatives were invited to take part in surveys and focus group discussions. This allowed us to develop a comprehensive understanding of their perceptions and needs of CR/SP services, facilitators and barriers for participating in CR/SP, as well as the acceptability of mHealth-based CR/SP services. Furthermore, surveys among medical staff were conducted to understand their

priorities, experience and preferences relating to CR/SP service development and provision. PPI also provided valuable information to help the research team to select the appropriate intervention delivery method, questionnaires and outcome measures, along with the burden of the intervention. The results of the study will be disseminated to PPI representatives and study participants who wished to be notified.

ETHICS AND DISSEMINATION

The Human Research Ethics Committee of Fudan University Zhongshan Hospital granted the primary ethics approval for the trial [HREC B2016-058]. The Curtin University Human Research Ethics Office granted the reciprocal approval for the trial [HRE2016-0120]. The report of the study will be disseminated via the usual scientific forums including peer-reviewed publications and presentations at national and international conferences.

DISCUSSION

The SMART-CR/SP study will evaluate the feasibility and impact of an innovative smartphone and WeChat-based home CR/SP program for patients with CHD after PCI therapy. We are not aware of any previously published studies that have reported the efficacy of a smartphone and social media CR/SP service delivery model.

Cardiac rehabilitation and secondary prevention is a Class I recommendation for the management of CHD patients.[33] However, despite the growing evidence of its cost-effectiveness[10] and efficacy in reducing cardiovascular morbidity and mortality[7], CR/SP services are limited in China. A recent national survey showed that only 30 of 124 (24%) large medical centres surveyed in China have operational CR programs, translating to approximately two programs per 100 million inhabitants.[15] To address this service provision

gap, there is a clear need to develop alternative delivery models to increase access to CR/SP services. Social media offers great potential for delivering health education and support through smartphones. Compared with past telephone and text message support, smartphones and social media may provide a more powerful, multi-functional platform for disease management. This includes access to step counting, multi-media messaging, voice/video call and group discussion. In China, and other LMICs, where access to tertiary and secondary prevention health care are often limited, these advanced technology functions may greatly facilitate the delivery of core components of modern CR/SP to many CHD patients who would not otherwise have had access to these important services. The potential reach of a smartphone and social media-based CR/SP intervention is great as it could easily be expanded to reach many smartphone and social media users at a low cost. Furthermore, this innovative service model could overcome common barriers to patients participating CR/SP program, such as inconvenience, geographical isolation and financial burden, [20 21 26] given it is easy to access, flexibility and low cost.

In conclusion, SMART-CR/SP will test the utility of a smartphone and WeChat-based intervention to deliver the core components of guideline advocated CR/SP. If the efficacy of this social media-based CR/SP intervention is validated, this will have significant potential to improve access to evidence-based CR/SP for patients with CHD. This is likely to translate to improved patient outcomes and reduced financial burden of CVD on health systems. Although the focus of this study is the delivery of a CR/SP intervention via smartphone and WeChat, there is great potential that this model of care could be adopted in both the primary and secondary prevention context for other chronic diseases, and using other social media platforms.

COMPETING INTERESTS

We declare that there are no conflicts of interest related to this clinical trial.

CONSENT FOR PUBLICATION

The manuscript does not contain any individual patient's data in any form.

FUNDING

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All blood pressure monitors were donated by Sky Innovation Technology (Shanghai) Limited, however, no staff from the company will be involved in the design, implementation and data analysis of the study. Significant 'in-kind' support (staff time) was provided by Fudan University Zhongshan Hospital.

AUTHOR'S CONTRIBUTIONS

TD and AM conceived the original concept of the study and wrote the first draft of the protocol manuscript. ZG, AS, LT, JW, YLC, KT, BKT, JBG contributed to the design of the study. All authors read and approved the final manuscript.

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PROTOCAL VERSION

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Table 1 Topic list of WeChat-based cartoon-format health education

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Secondary outcomes					
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Lipid profile	Fasting blood sample	✓	✓	✓	✓
Medication adherence	Adherent to cardiac-protective medications	✓	✓	✓	✓
Smoking	Self-report	✓	✓	✓	✓
Obesity	Weight, height, waist and hip circumference	✓	✓	✓	
Physical activity	General Physical Activity Questionnaire[46]	✓	✓	✓	✓
Fruit and vegetable intake	WHO Steps instrument[44]	✓	✓	✓	✓
Anxiety symptoms	Generalized Anxiety Disorder 7-item (GAD-7) scale[47]	✓	✓	✓	✓
Depressive symptoms	Patient Health Questionnaire (PHQ-9)[48]	✓	✓	✓	✓
Quality of life	SF-12_V2™ Health Survey[49]	✓	✓	✓	✓
CV events	CVD death, non-fatal AMI, stroke or hospital admission with unstable angina or congestive heart failure		✓	✓	✓
CR/SP needs survey	Patient needs for the core components of CR/SP [33]	✓	✓	✓	✓
All-cause mortality	Data from CDC		✓	✓	✓

6MWT, six minute walk test distance; CHD, coronary heart disease; CR/SP, cardiac rehabilitation and secondary prevention; AMI, acute myocardial infarction; BP, blood pressure; CV, cardiovascular; LDL, low-density lipoprotein; WHO, World Health Organization; CDC, Centre Disease Control and Prevention.

Figure 1 : Randomised controlled trial design and flowchart. The control group will receive usual care but no formal CR/SP. The intervention group will receive a smartphone and WeChat-based CR/SP program providing education and support for risk factor monitoring and modification.

CHD, coronary heart disease; PCI, percutaneous coronary intervention; CR/SP, cardiac rehabilitation/secondary prevention; CVD, cardiovascular disease; 6MWT, six-minute walk test; CR/SP, cardiac rehabilitation and secondary prevention; LDL, low-density lipoprotein

Figure 2 Components of the Smart-CR/SP system

SMART-CR/SP incorporates core components of modern CR/SP: physical activity tracking with interactive feedback and goal setting; education modules addressing CHD understanding and self-management; remote blood pressure monitoring and strategies to improve medication adherence. Furthermore, a dedicated data portal and a CR/SP coach will facilitate individualised supervision and counselling.

Figure 3 WeChat-based CR/SP system interface depicting health education(a), physical activity tracking(b), blood pressure monitoring(c), cholesterol management(d), medication management(e), individual counselling(f), smoking secession(g), mental health(h)

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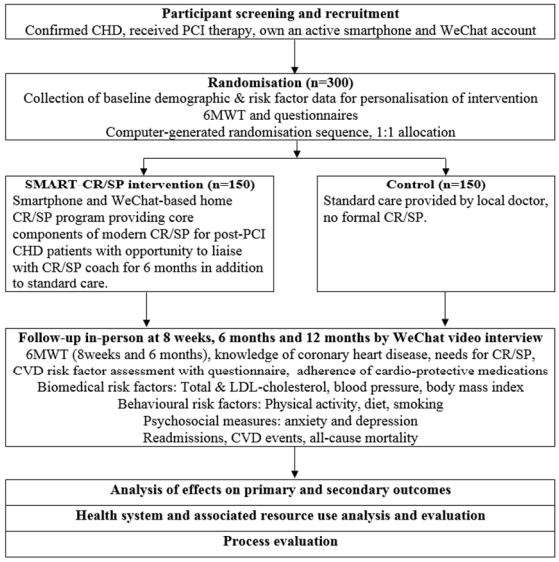

Figure 1. Randomised controlled trial design and flowchart. The control group will receive usual care but no formal CR/SP. The intervention group will receive a smartphone and WeChat-based CR/SP program providing education and support for risk factor monitoring and modification.

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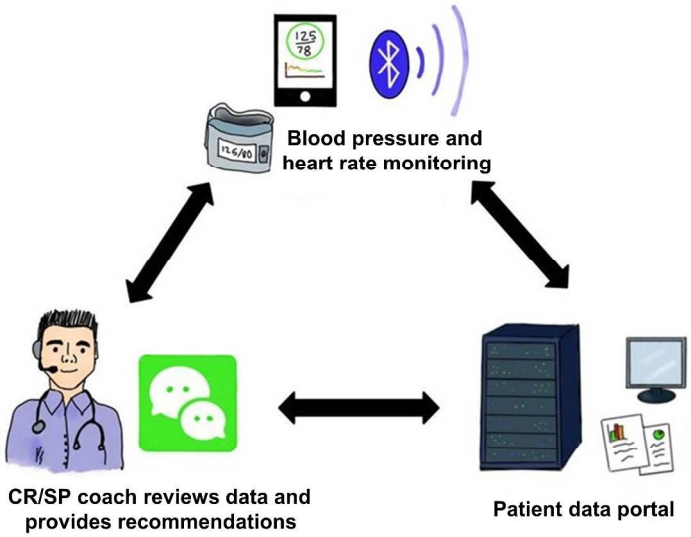

Figure 2. Components of the SMART-CR/SP system: physical activity tracking with interactive feedback and goal setting; education modules addressing disease understanding and self-management; remote blood pressure monitoring and strategies to improve medication adherence. Furthermore, a dedicated data portal and a CR/SP coach will facilitate individualised supervision and counselling.

338x190mm (300 x 300 DPI)

Figure 3. SMART-CR/SP system interface depicting health education(a), physical activity tracking(b), blood pressure monitoring(c), cholesterol management(d), medication management(e), individual counselling(f), smoking secession(g), mental health(h)‼ ┼ ‼ ┼

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 16
	5b	Name and contact information for the trial sponsor	16
	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	16
	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)	NA

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	5-6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
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)	6

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	7
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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	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)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
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	12
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 (see Figure)	12

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	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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 enrol participants or assign interventions	8
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8-9
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	11
	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	14

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	14
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	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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)	14
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	14
	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	14
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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16-17
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)	16-17

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16-17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
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	14
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	NA
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	17
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.