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Trial Design

I-CARE randomized clinical trial integrating depression and acute coronary syndrome care in low-resource hospitals in China: Design and rationale

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ABSTRACT

Depression and acute coronary syndromes (ACS) are both common public health challenges. Patients with ACS often develop depression, which in turn adversely affects prognosis. Low-cost, sustainable, and effective service models that integrate depression care into the management of ACS patients to reduce depression and improve ACS outcomes are critically needed. Integrating Depression Care in ACS patients in Low Resource Hospitals in China (I-CARE) is a multicenter, randomized controlled trial to evaluate the efficacy of an 11-month integrated care (IC) intervention compared to usual care (UC) in management of ACS patients. Four thousand inpatients will be recruited and then randomized in a 1:1 ratio to an IC intervention consisting of nurse-led risk factor management, group-based counseling supplemented by individual problem-solving therapy, and antidepressant medications as needed, or to UC. The primary outcomes are depression symptoms measured by the Patient Health Questionnaire-9 at 6 and 12 months. Secondary endpoints include anxiety measured by the Generalized Anxiety Disorder-7; quality of life measured by the EQ-5D at 6 and 12 months; and major adverse events including the combined end point of all-cause death, suicide attempts, nonfatal myocardial infarction, nonfatal stroke, and all-cause rehospitalization at yearly intervals for a median follow-up of 2 years. Analyses of the cost-effectiveness and cost-utility of IC also will be performed. I-CARE trial will be the largest study to test the effectiveness of an integrated care model on depression and cardiovascular outcomes among ACS patients in resource-limited clinical settings.

Cardiovascular disease (CVD) and serious mental illness are major health challenges in China and throughout the world[1]. CVD is the leading cause of death globally and currently accounts for >40% of all deaths in China.[2] Acute coronary syndromes (ACS) are especially serious manifestations in China, with in-hospital mortality of nearly 5% for admitted patients.[3] The burden of serious mental illness also is increasing and is projected to become the second leading cause of disability-adjusted life years (DALYs) lost worldwide by 2020 and is expected to be the number 1 cause of DALY loss globally by 2030.[4, 5]It has been estimated that the prevalence of all mental disorders is 17% and that of serious mental illness is 1% in China.[6]

Comorbid occurrence of major depression and CVD is common and adversely impacts clinical outcomes, as well as economic outcomes resulting from diminished productivity and increased health

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Table 1
Schedule of data collection.

Items	Sources	Baseline	6-m follow-up	12-m follow-up	End of study
Demographics (age, sex, education, employment)	Survey	X			
Diagnosis and subtypes of ACS	Medical record	X			
Medical insurance	Survey	X			
Disease history (CVD, depression, etc)	Medical record	X			
Lifestyle (smoke, alcohol use, sleep, physical activity)	Survey	X	X	X	
Height, weight, & heart rate	Medical record	X	X	X	
Blood pressure	Medical record	X	X	X	
Blood lipids	Medical record	X	X	X	
Blood glucose	Medical record	X	X	X	
Suicide risk assessment (BDI-II item 9)	Survey	X	X	X	
Social support assessment (ESSI, PSSS)	Survey	X	X	X	
Quality of life (EQ5D)	Survey	X	X	X	
Depression assessment (PHQ-9, BDI-II)	Survey	X	X	X	
Anxiety assessment (GAD-7)	Survey	X	X	X	
Antidepressant medication use	Survey/medical record	X	X	X	X
ACS secondary prevention medication use	Medical record	X	X	X	X
Cost of hospitalizations	Medical record	X	X	X	
MAEs	Medical record	X	X	X	X

ESSI, ENRICHD Social Support Inventory; *PSSS*, Perceived Social Support Scale; *MAEs*, major adverse events.

expenditures.[7, 8] Although estimates of major depression occurring in post-ACS patients in the United States range from 15% to 20%, an additional 20% of patients report increased depression symptoms without being diagnosed with depression disorder.[9, 10] In China, it has been estimated that the prevalence of depression symptoms in hospitalized patients with CVD ranges between 28% and 90%.[11-13]

Previous studies have concluded that depression treatment in CVD patients is generally associated with modest improvements in depression symptoms, but there is little evidence that improvements in depression result in better clinical outcomes.[14-18] Moreover, there are few low-cost and scalable service models that integrate depression treatment and ACS care to reduce depression and improve cardiovascular outcomes.

The overall aim of the Integrating Depression Care in ACS patients in Low Resource Hospitals in China (I-CARE) study is to develop, implement, and evaluate a nurse-coordinated depression care model integrated into the care of ACS patients in low-resource settings in China, with rigorous evaluation of feasibility, acceptability, effectiveness, and cost-effectiveness. The specific aims are to determine the effectiveness of the integrative care (IC) in comparison to usual care (UC) in reducing depression symptoms, improving cardiovascular outcomes, improving quality of life, and reducing medical expenses. Potential mediators and possible modifiers of the effect of the IC model will also be examined.

Methods

Study design overview

I-CARE is a randomized controlled trial evaluating the IC model in 20 hospitals drawn from the well-established research network of the Clinical Pathways for Acute Coronary Syndrome in China studies. The study was approved by the Institutional Review Board of Peking University, and all study patients will provide written informed consent. The trial is registered on clinical trials.gov (NCT02195193).

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Patient population and eligibility

Patients who meet the following inclusion and exclusion criteria will be recruited by their treating physicians according to the information from medical records or direct communication with patients during their index ACS hospitalization.

Inclusion criteria

ACS includes ST-elevation myocardial infarction, non–ST-elevation myocardial infarction, and unstable angina. Participants will be at least 21 years old, and the ACS will be judged to be stable at the time of study enrollment.

Exclusion criteria

1. Severe CVD or medical comorbidity that indicates the patient's life expectancy is less than 12 months (eg, New York Heart Association class IV heart failure, terminal cancer)
2. Seriously disabled (unable to travel to the hospital for follow-up treatment)
3. Suffering from problems that affect normal communication (eg, intellectual impairment, aphasia, observed mental confusion suggesting dementia, deafness)
4. Nonpermanent resident or permanent resident planning to move out of the region within 12 months
5. Pregnant or breast-feeding or planning pregnancy within 12 months
6. Established diagnosis of bipolar disorder, schizophrenia, psychotic depression, or acute suicidality.
7. Alcohol dependence
8. Unable to provide written informed consent

Data collection

Data collection will be conducted at baseline and at 6 and 12 months after discharge by study staff independent of the nurse trained to provide the IC intervention. Study staff will be blinded to the intervention group. Data will be entered into a Web-based IT system that is centrally managed.

Baseline assessments will be completed prior to randomization. Patients will provide sociodemographic information and lifestyle habits. The medical records will be reviewed to collect information on medical history, medical treatments administered during admission and at hospital discharge, and physical measurements. For depression assessment, we will use the 9-item Patient Health Questionnaire (PHQ-9).[19, 20] Item 9 (suicidal ideation) from the Beck Depression Inventory-II (BDI-II) also will be administered to assess suicidal risk.[21, 22] To assess social support, all patients will complete the ENRICHD Social Support Inventory.[23] The General Anxiety Disorder−7 (GAD-7) also will be used to detect generalized anxiety disorder.[24] Quality of life will be assessed using EQ5D.[25]

We selected these instruments because they are simple and easily administered by trained lay persons at our participating hospitals. Because of budgetary constraints, we also plan to administer the 21-item

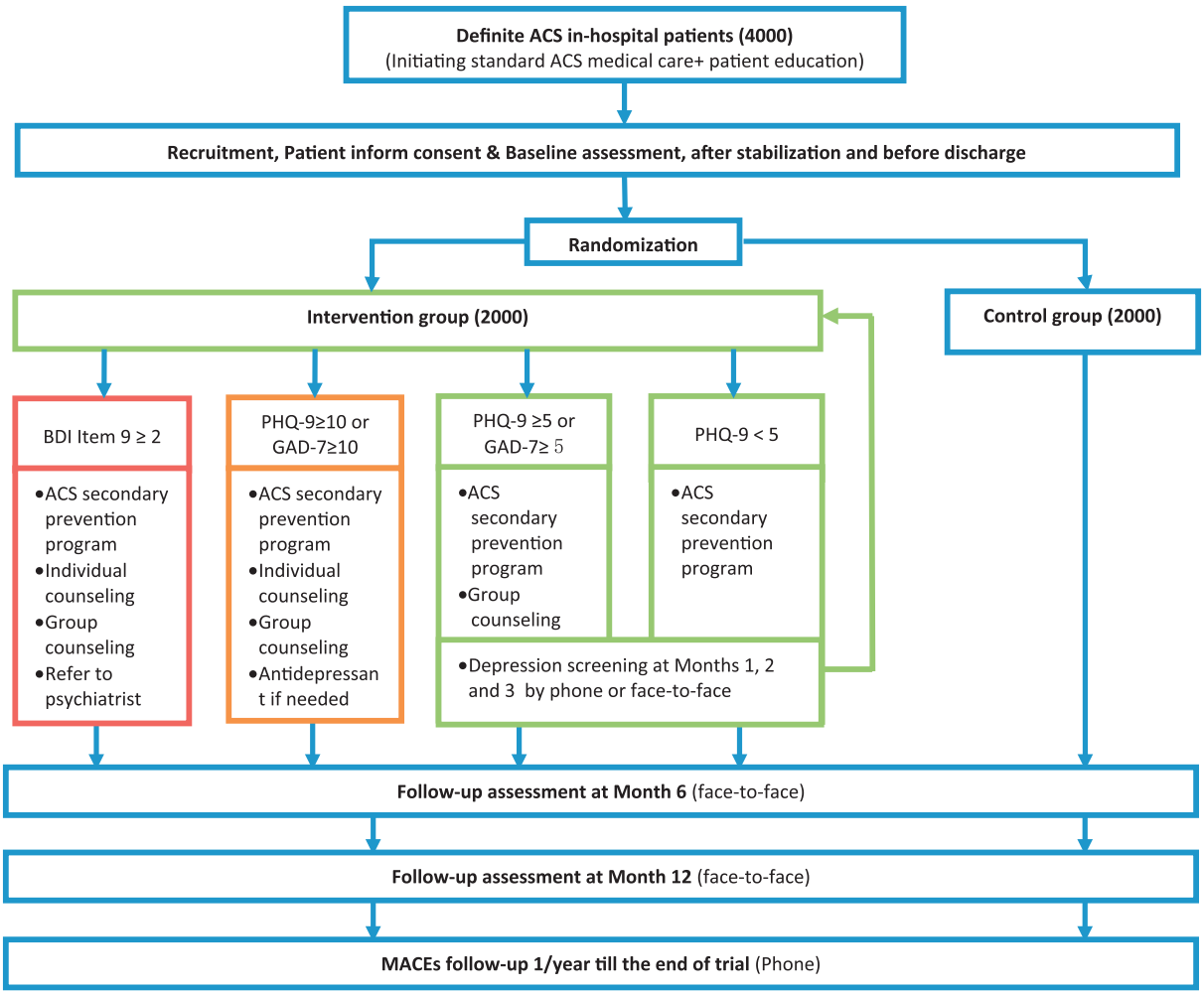

Figure 1. Flowchart of randomization, intervention, and follow-up. *MAEs*, major adverse events.

BDI-II[21] and the 12-item Perceived Social Support Scale[26, 27] to a subset of 800 patients from 4 preselected hospitals.

Participants will return at 6 and 12 months for postdischarge follow-up assessments, and the same information that was obtained at baseline will be collected (Table 1). Additionally, medication adherence and major adverse events (including all-cause deaths, suicide attempts, nonfatal myocardial infarction, nonfatal stroke, and all cause rehospitalization after discharge) also will be obtained from patient reports and confirmed from medical records. In addition, medical event data will be collected annually until the last enrolled patient has completed 1 follow-up, with an anticipated median follow-up period of at least 2 years.

Randomization and interventions

Randomization will be performed centrally by the Web-based IT system. We will use permuted-block randomization, stratified by hospital and PHQ-9 score (<10 or ≥10), with a random size of blocks of 4, 6, and 8. Patients will be randomized in a 1:1 ratio into 1 of 2 groups: IC or UC. Figure 1 depicts the study design.

Study interventions

Standard care in both IC and UC

Prior to randomization, patients will receive standard care and health education during their hospitalizations. We will use the Clinical Pathways for Acute Coronary Syndrome in China phase 3 study interventions as standard ACS care, which were developed in conjunction with the Chinese Society of Cardiology and are based on relevant American Heart Association and American College of Cardiology guidelines.[28, 29] The interventions include the following 6 components: establishing a quality of ACS care improvement leadership group in each hospital; implementing tailored guideline-based clinical pathways; training the local cardiologists by "train-the trainers" model and online education program; using a centrally managed Web-based system to collect data and feedback on the key performance indicators on quality of ACS care assessment every 6 months; and providing online expert consultation and distributing a patient education brochure on ACS secondary prevention. Details had been published previously.[30]

Usual care

Other than implementation of the standard ACS care, no attempt will be made to influence the management of patients randomized to UC. However, any patient who obtains a BDI-II item 9 score ≥2 at either the 6- or 12-month follow-up assessments will be referred to a local mental health provider.

IC intervention

In addition to the standard ACS care, patients randomized to the IC group will receive the integrated intervention, provided primarily after hospital discharge. The IC model will be delivered by a collaborative team composed of cardiologists and nurses in the department of cardiology in the participating hospital (Figure 2). The cardiologist and

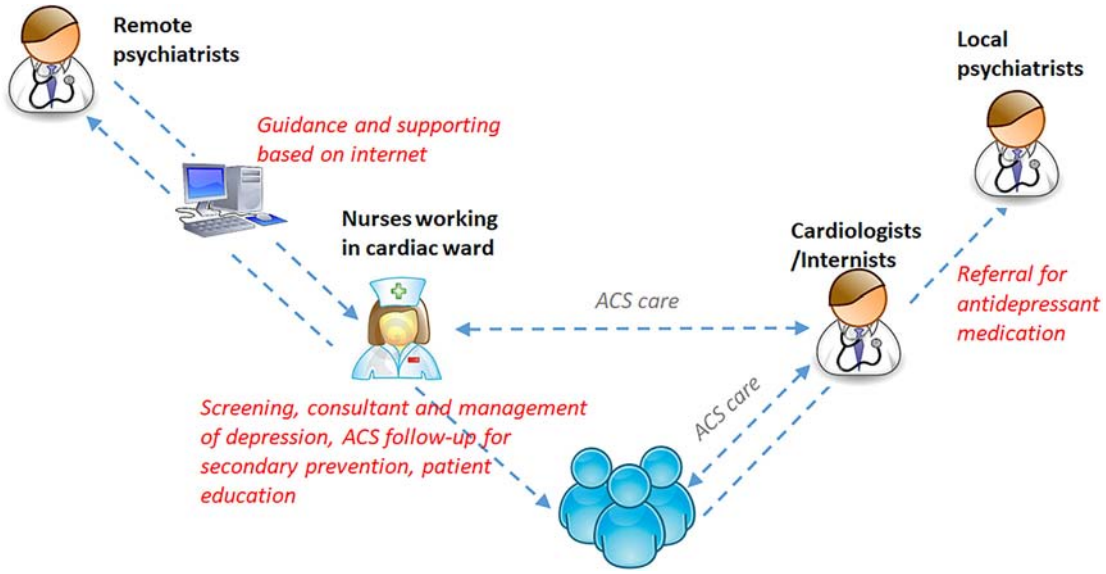

Figure 2. A nurse centralized Web-based integrated care model for comorbidity patients with depression and ACS.

the nurse will be responsible for the long-term care relating to both depression and ACS secondary prevention.

ACS secondary prevention program

The ACS secondary prevention in the integrated model of care includes the following:

1. ACS medication adherence, home blood pressure, and therapeutic lifestyle changes checked and reinforced by the nurse before discharge and at months 1, 2, 3, 5, and 11 after discharge. If needed, cardiologists will provide continuing prescriptions or medication adjustments.
2. Clinic follow-up visit with measurements of blood pressure, weight, fasting serum cholesterol, and blood glucose/HbA1c will be recommended at months 2, 5, and 11.
3. For patients attending group counseling, the first 15 minutes of each session will be dedicated to educating patients about ACS, risk factors, and secondary prevention medications. The remaining time will be devoted to depression care.
4. At each group and individual counseling session, the nurse also will measure blood pressure and body weight

Comorbid depression care program

The depression treatment includes 5 key elements: screening for depression and anxiety; group counseling; individual counseling; and referral for antidepressant medications and, if needed, immediate treatment for acute suicidality (after randomization).

1) Screening of depression and anxiety: Patients in the IC group will be screened additionally for 3 times using PHQ-9 and GAD-7 at months 1, 2, and 3 after discharge by the nurse by phone or face-to-face. Patients identified as having a PHQ-9 score ≥ 10 or a GAD-7 ≥ 10 at any of the 4 screening visits will be enrolled in the individual counseling intervention. Otherwise, the patient will be screened again until either the above criteria are met or until all 4 screens are completed.
2) Classification of patients for initiating different components of the depression care

We will use the following criteria to initiate the different components of IC:

- All IC patients who have PHQ-9 score ≥ 5 or GAD-7 score ≥ 5 at any of the 4 assessment time points will be referred to group counseling.
- All IC patients who have PHQ-9 scores ≥10 or GAD-7 score ≥ 10 at any of the 4 assessments will be contacted, and individual counseling will be offered. If a patient receiving individual counseling has a decrease in PHQ-9 score of <25% or a PHQ score ≥10 after 5 individual consultations, they will be referred to a specialist for antidepressant medication.
- Any patient who obtains a BDI-II item 9 score ≥ 2 at any of the 4 assessments or during the treatment of depression will immediately be evaluated for acute suicidality and, if necessary, will be referred to a local mental health center or specialist.

Group counseling. A 4-session group counseling intervention will be provided to all eligible patients by a trained nurse. The group counseling will be conducted once a month for 4 months. Family members or caregivers will be welcome to attend, with patients' consent, in order to increase patient adherence to the treatment as well as to enhance social support and promote greater awareness about depression and anxiety among family members and the community.

Each group session will last for 90 minutes and will be manualized with specific goals, including to foster mutual trust and help patients better understand why they experienced a cardiac event (session 1), learn skills of coping with stress (session 2), and learn strategies to improve social support (session 3) and techniques to reduce negative emotions (session 4).

Individual counseling: problem-solving therapy. All IC patients identified as having a PHQ-9 ≥ 10 or a GAD-7 ≥ 10 from the study screening procedure will receive individual counseling sessions provided by the nurse. The nurse will use problem-solving therapy to help patients and set goals for improved ACS medication adherence and self-care (eg, exercising and self-monitoring of blood pressure). Face-to-face meetings are preferred for individual counseling, and if patients are unable to visit the nurse, the counseling will be provided by telephone. The individual counseling will occur biweekly for at least 4 sessions and monthly for other sessions depending on therapeutic effects and patients' preferences.

Selection and training of nurse interventionists

The intervention nurses were selected with recommendations by the participating hospital directors and telephone interviews by the study management team to maximize the likelihood for delivering the intervention at high levels of fidelity.

Selected nurses will participate in a 6-day face-to-face central training program including case studies and simulations. Out of the 6-day training program, 2 days will be dedicated to depression symptom care with problem-solving therapy, 2 days to semistructured group counseling, 1 day to ACS care, and 1 day to the implementation of the integrated care model. Initial certification will be awarded based on the nurse's performance on the assignments during the training.

After the formal intervention is launched, the nurse will be required to tape-record each individual session of her first patient and video-record all the 4 sessions of the first group. Records will be reviewed by the study psychiatrists, and certification will be awarded if the nurse passed the professional's reviews. Otherwise, the nurse will be asked to record the next patient/group until the study psychiatrist was satisfied. In addition, the nurse will receive 1-hour Web-based supervision biweekly from the study psychiatrists as continuous training until both the study psychiatrist and the nurse are comfortable with her ability to reduce the frequency of supervision. Thereafter, the frequency of online or field supervision and training will depend on need determined by the study psychiatrist.

Outcome measures

This study will collect information on primary and secondary outcomes to evaluate the intervention and demonstrate benchmarks of success. The primary outcomes will be changes in mean PHQ-9 scores from baseline to 6 and 12 months. The PHQ-9 was selected for its ease of administration and understanding by patients with little formal education and because it was suggested as a useful screening instrument for depression.[31]

Secondary outcomes include the following: (1) incidence of major adverse events (MAEs) including all-cause death, suicide attempts, nonfatal myocardial infarction, nonfatal stroke, and rehospitalization for any reasons after discharge; (2) proportion of patients with PHQ-9 < 5 at 6 and 12 months; (3) proportion of patients with self-reported adherence to evidence-based ACS secondary prevention treatment at 6 and 12 months (single and combination use of aspirin/clopidogrel, statin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and/or β-blocker); (4) quality of life (EQ5D) at 6 and 12 months after discharge; (5) proportion of patients with improved cardiovascular risk surrogates (blood pressure <140/90 mm Hg, heart rate <70 beats/min, serum low-density lipoprotein cholesterol <100 mg/dL, and blood sugar <7.0 mmol/L; individually or in combination) at 6 and 12 months after discharge; and (6) proportion of patients with increased healthy lifestyle (a global measure including physical activity ≥3 times/wk and more than 30 minutes each time, no smoking, no alcohol use, and body mass index <24 kg/m^2) at 6 and 12 months after discharge.

Masking

We will take several measures to mask the assessors from participants' group assignment. First, all baseline assessments will be performed prior to randomization, so the assessors (and all study staff) would be unaware of patients' treatment group before the interventions initiated. Second, the assessors will be different from the interventionists, and the Web-based IT system will automatically inform the interventionist which patient is included in the intervention group, eliminating any communication between the assessors and interventionists about the group assignment. Third, we will require the assessors to not ask which treatment the patients received in the follow-up assessments. Fourth, study interventions generally will take place outside of the hospitals, which will prevent patients from being aware of the other intervention. Lastly, there will be no overlap in responsibilities by assessors and interventionists, and staff will be reminded not to share patient research information during the trial. We do not have a procedure to determine if accidental unmasking occurs; however, we believe the chances of unmasking will be small.

Sample size considerations

The sample size for this study will be 4,000 participants. For the primary outcome, we expect 94% power at 6 months and 91% power at 12 months ($\alpha = 0.05$) to detect a difference of mean change in PHQ-9 scores with a moderate-large effect size (0.7) between IC and UC groups with a pooled SD of 6. The loss to follow-up at 6 and 12 months is estimated to be 10% and 20% respectively.

Statistical analysis

Our primary analysis will follow the intention-to-treat principle. Patient characteristics will be described by treatment allocation. For the efficacy analysis, patient outcomes at baseline and at 6 and 12 months will be included in a longitudinal model with random slopes and random intercepts. Random effects for hospitals will be incorporated. Initially, patient trajectories will be assessed as to whether they are linear. If not, additional terms may be needed to describe the average trajectories. The treatment effect will be represented by an interaction between time and treatment group. Patient- and system-level factors that are thought of as clinically significant will be further adjusted for secondary analysis for all outcomes. Other continuous outcomes, GAD-7, BDI-II, and EQ5D score change, will be analyzed using the same methods as described for the primary outcome. For the binary outcomes, such as proportion of patients with PHQ-9 ≥ 5 at 6 or 12 months postdischarge, proportion of patients with self-reported adherence to evidence-based ACS secondary prevention treatment at 6 and 12 months, etc, generalized linear mixed models will be used to get the overall estimate of intervention effect.

For the incidence of MAEs during follow-up, the Kaplan-Meier curves will be plotted by treatment allocation, and log-rank test will be used to detect the difference of event rate between 2 groups.

For the primary outcome, we will also test if the intervention effect is modified by severity of depression at baseline, type of ACS, age, gender, and social support indicators.

Statistical analyses will be carried out using the SAS Enterprise Guide 7.13 (SAS Institute Inc, Cary, NC).

Data and safety monitoring plan

The study will be monitored regularly by a professional management team at The George Institute, China, on the patient recruitment, fidelity of the intervention, depression screening and assessment, data collection, and follow-up events. Patient data in the online database are protected by password and only available to authorized users. Deidentified data will be used for data analysis.

A Data and Safety Monitoring Board (DSMB) will be established and will be composed of experts in cardiology (Y. S.), psychiatry (T. S.), and biostatistics (Y. C.). The DSMB will meet annually to monitor adverse events including deaths, MAEs, and suicides. In the event of unexpected significant risks to study subjects, the DSMB may recommend to stop the trial early. Otherwise, the study will continue to the end, and no interim analysis is planned.

Cost-effectiveness evaluation

We will conduct both cost-effectiveness and cost-utility analyses from the health sector perspective. Intervention costs will include the cost of all resources needed to reproduce the program such as training costs and personnel but will exclude any research and development costs. For all patients (both in the intervention and control group), cost of hospitalizations postdischarge will be obtained through the patient unique identifiers and estimated by average costing with

adjustment for regional variations. Incremental cost-effectiveness ratios with estimation of confidence intervals by nonparametric bootstrapping method will be calculated in terms of the incremental cost per additional patient free from depression at 12 months and (exploratory) per MAE averted within 12 months postdischarge. Additional modeling based on evidence from the literature of disease progression and long-term treatment effects will be conducted to extrapolate these trial-based cost-effectiveness findings into estimates of cost per DALY averted. Cost-utility analysis will be conducted in terms of quality-adjusted life year gained. We will use the World Health Organization criterion to judge the intervention for the value for money.[32] One-way sensitivity analysis will be conducted around key variables, and a probabilistic sensitivity analysis will estimate the joint uncertainty in all parameters.

Process and qualitative evaluation

A formal process evaluation will be conducted after the intervention is completed to detect any possible impacts of the intervention that are not be able to obtained from the randomized controlled trial, to understand possible barriers and facilitators that may influence the implementation of the intervention. We will select 6 hospitals representing high-performing, average-performing, and low-performing hospitals, with 2 hospitals in each category to participate in this evaluation. The evaluations will be based on in-depth interviews with (1) intervention nurses, (2) cardiologists, (3) patients, and (4) family members involved in the study.

Current status

The study recruitment had been completed at the end of January 2017. A total of 4,042 patients hospitalized with ACS were recruited from 16 hospitals: 2,014 in intervention and 2,002 in control. As of May 10, 2017, 3,269 (81%) had completed the 6-month follow-up, and 2,277 (56%) had completed the 12-month follow-up. The final follow-up will be completed by the end of February 2018.

Discussion

China is the most populous country in the world, and it has a vast health care system; however, the service capacity per capita is insufficient, and there is significant disparity between urban cities and rural counties, with 2.14 physicians per 1,000 people in large cities compared with 0.75 in rural counties.[33] The situation is even worse with respect to mental health services. The total number of licensed psychiatrists (including assistants) in 2015 was about 2.0 psychiatrists per 100,000, 4.2 psychiatric nurses per 100,000, and no social workers, representing only 1% of health personnel in China[34,35]—well below the number of mental health professionals in the United States (12.4 psychiatrists per 100,000, plus 30 psychologists per 100,000 and 60 social workers per 100,000) and also lower than the global median 9 mental health workers per 100,000 in 2014.[36] Psychiatric resources are concentrated in large cities in developed areas. There are 492 psychiatry hospitals in large cities and only 145 psychiatry hospitals in counties, accounting for 3.5% and 2.4% of all hospitals, respectively.[33] The relative absence of mental health services, especially in rural areas of China and in the nonspecialist services, regardless of the presence or absence of CVD, cannot be addressed by the current service delivery model within the Chinese health system. An innovative model that allows task shifting from specialist service providers to nonspecialist providers is urgently needed to address this personnel shortage and expand the resources devoted to the prevention and treatment of psychiatric conditions.

Typically, Chinese patients with comorbidity of chronic disease and mental illness are usually only receptive to the treatment of their medical (ie, nonpsychiatric) condition. Few patients receive psychiatric treatment because of the scarcity of mental health service resources and/or the significant cultural stigma against mental disorders. Our integrated model provides an opportunity to increase the awareness, availability, and service accessibility by screening, diagnosis, and treatment of these patients by nonpsychiatric nurses in the cardiology departments, which could be a solution to improve the mental health services in rural area in the future. The model also may be more easily accepted by patients who are culturally unwilling to be treated by traditional mental health professionals. Our model also shifts clinical practice from isolated into integrated. Previous work around the world has shown that task shifting to health care workers without specialist certifications for many health conditions including mental health can be an effective strategy when properly tailored to the local context.[37–40] To our knowledge, I-CARE will be the first large trial to test the effectiveness of this model in resource-limited settings and will add evidence to the existing literature which primarily comes from the United States and other developed countries,[14-18] and also provides a treatment model for developing countries that addresses comorbid chronic diseases and mental illness.

In summary, the I-CARE study provides an opportunity to develop, implement, and rigorously evaluate an innovative health service model which integrates mental health screening and treatment with treatment for ACS in resource-constrained hospitals in China. This innovative, flexible, and sustainable model, if tested to be effective in improving mental health status or/and improving physical outcomes, can potentially be applied to a variety of chronic medical conditions.

Disclosure

All authors have no conflicts of interest to disclose and have approved the final article. The authors are solely responsible for the design and conduct of this study, the data analyses, the drafting and editing of the manuscript, and its final contents.

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