SIMPLIFIED CARDIOVASCULAR MANAGEMENT STUDY

A Cluster-Randomized Trial to Evaluate the Effects of a Simplified Cardiovascular Management Program in Tibet, China

China International Centre for Chronic Disease Prevention

Tibet University

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Abstract

Cardiovascular disease (CVD) is the leading cause of morbidity, mortality, and disability in not only developed, but also developing nations. There are many well-established interventions such as lifestyle modifications and prescription of appropriate medications that along with their consistent use can help avert much of these burdens if the practicalities of how to deliver such care to large numbers in resource-poor settings at low cost can be resolved.

The **overall goal** of the present proposal is to develop, pilot test, and evaluate a highly simplified, but guideline-based program for cardiovascular management in resource-scarce settings. The **specific aim** is to evaluate the effects of implementing a simple low-cost cardiovascular management program for high-risk individuals, delivered by primary care providers and community healthcare workers (CHWs), including looking at the proportion of patients appropriately treated with diuretics and aspirin. A number of secondary outcomes will also be measured. The main features of the **simplified cardiovascular management program** include: 1) focus on high-risk patients for maximal cost-effectiveness; 2) simplified yet evidence-based measures; 3) systematic training of CHWs; 4) healthcare system strengthening with electronic decision support and performance feedback and payment; 5) adaptive interventional design; and 6) local government support.

A cluster-randomized controlled interventional pilot trial will be conducted in the rural areas of Tibet, China. A total of 23 villages from 10 townships in Gongbujiangda County and Linzhou County will be selected to be randomized to receive the intervention (12 villages; 8 from Gongbujiangda, 4 from Linzhou County) or usual care (11 villages; 7 from Gongbujiangda County, 4 from Linzhou County). Before the start of the intervention, screenings will be performed at each village to identify the number of high-risk individuals in each of these villages. The intervention will then be implemented in the randomly selected intervention villages and last for one year. Afterwards, a post-intervention assessment of all high-risk individuals will be conducted. **Process evaluation** and **economic evaluation** represent important aspects

of the evaluation matrix that will also be performed. The results of the study are expected to both advance scientific knowledge to prepare for future large-scale studies and provide translational evidence necessary for sound policy making to address the CVD burden in resource-scarce settings.

LIST OF ACRONYMS

CoE: Centre of Excellence

CHW: Community Health Workers

CVD: Cardiovascular Disease

EDS: Electronic Decision Support

ICC: Intra-cluster correlation coefficient

PCP: Primary Care Provider

1. Background, Aims and Innovation

1.1. Background

Cardiovascular disease (CVD) is the leading cause of morbidity, mortality, and disability in not only the developed but also developing nations[1-4]. There are many well-established interventions such as lifestyle modifications, appropriate prescription utilization, and consistent use of aspirin and low-dose diuretics that can help avert much of these burdens if the practicalities of how to deliver care to large numbers in resource-poor settings at low cost can be resolved[5-16]. One particularly cost-effective approach for secondary prevention of CVD is to identify and manage individuals at high cardiovascular disease risk in order to prevent or delay events[17-24]. This approach has been tested in the Rural Andhra Pradesh Cardiovascular Prevention Study (2007-2010) [25] in India and is currently being implemented in the China Rural Health Initiative (2010-2013) funded by the NHLBI.

Building on our collective previous experiences, we propose to extend this kind of translational intervention research to areas with even more limited economic and healthcare resources but nevertheless high CVD burdens. The management program needs to be standardized and based on established guidelines, but further simplified to suit local situations. The proposed simplified and yet evidence-based management program will serve as a starting point to address the lack of initiatives to combat CVD in these areas and to enhance capacity at the grass-root level. It will also be designed with built-in mechanisms to easily expand into more comprehensive programs for CVD prevention once there are more resources to do so.

1.2. Aims

The **overall goal** of the present proposal is to develop, pilot test, and evaluate a highly simplified but guideline-based program for cardiovascular management in resource-scarce settings. The **specific aim** is to evaluate the effects of implementing a simple low-cost cardiovascular management program for high-risk individuals, delivered by primary care providers (PCPs) or community healthcare workers (CHWs), on the

proportion of patients appropriately treated with diuretics. A number of secondary outcomes will also be monitored in resource-scarce settings in rural China.

1.3. Innovation

The innovations in this research are four-fold. First, the project bridges a major gap in translational research on how to apply well-established approaches from scientific research to real world settings in preventing and managing CVD. Second, the focus of the project will be on rural areas in developing countries with high CVD burdens but even more scarce healthcare resources than most other rural areas. There are some published literature[26-27] and existing programs[25] evaluating how to translate scientific evidence into effective CVD management in relatively resource-poor settings at the grass-root level. To the best of our knowledge, none has focused specifically on these issues in areas with extremely limited resources. Third, the intervention is designed to pioneer a unique combination of selective measures based on clinical guidelines. These measures are deemed to be particularly low-cost and effective based upon existing evidence collected mostly from developed countries.[18-19] Whether the cost-effectiveness of these measures and the practicality of how to implement these measures holds true in resource-scarce areas in developing countries remain to be tested. Fourth and finally, we aim to improve CVD prevention and management through strengthening of the healthcare system by integrating and developing the capacity of PCPs and CHWs[28-31] via training, electronic decision support (EDS)[32-34], performance feedback[35-36], and performance-based payment.[37-38] These measures are designed to be both cost-effective and scalable in the future if translated into health policies.

2. Significance and Public Health Impact

2.1. Significance

Many regions in developing countries are now characterized as having triple burdens which include the longstanding problem of infectious diseases, the rapidly rising burden of non-communicable chronic diseases, and the serious lack of economic and healthcare resources coupled with a weak healthcare system incapable of dealing with health problems on a widespread scale[39-41]. While evidence-based national and

international guidelines on managing chronic conditions such as hypertension, coronary heart disease, and stroke are well-established[5-16, 42], cost-effective approaches suitable for adoption in triple-burden areas in developing countries have not been adequately investigated or well understood. The proposed project aims to address the highly prevalent problem of CVD in the remote and poor areas[42-46]of China that has of yet not received commensurate attention so far. The interventional model is designed to overcome inherent barriers to prevention and management of CVD in these areas such as extremely limited economic resources, lack of public awareness of the problem, and lack of trained healthcare professionals[47]. Therefore, the results of the study are expected to both advance scientific knowledge and to provide translational evidence necessary for sound policy making to address the CVD problem in resource-scarce settings.

2.2. Public Health Impact

Employing a high-risk approach is one of the two commonly used methods for addressing public health problems[48]. Due to the high prevalence of CVD, high event and fatality rates of CVD patients, and the resulting large medical costs, prevention of CVD focusing on existing patients and individuals at high cardiovascular risk is considered to be cost-effective in places with low public awareness of the problem and limited available resources to address these issues[22, 48]. Though not a population-wide approach, the high prevalence of high-risk persons in these places[43, 46] means that the interventions have the power to improve the health of large numbers of people in interventional areas. Given the enormous need to prevent CVD in many poor countries and regions around the globe [47], if successful interventional models can be implemented centrally through policy change in suitable regions, they can positively influence the health of even larger numbers of individuals at low overall cost and with very high cost-effectiveness.

3. Study Design

This pilot project is a cluster-randomized controlled interventional trial conducted in the rural areas of Tibet, China. A total of 23 villages in 10 townships from 2 counties

(Gongbujiangda County and Linzhou County) in Tibet will be selected to be randomized to receive the intervention (12 villages) or usual care (11 villages). The main intervention is a simplified cardiovascular management program for high-risk individuals delivered by village CHWs with support of PCPs (county physicians or township physicians). Research personnel training, implementation and monitoring the interventions and the assessment of the study outcomes will be identical in each study site. All outcome assessments will be done in exactly the same way in every village, regardless of its assignment to intervention or control. Before the intervention begins, a village-wide screening will be done to identify high-risk individuals in the selected villages. Afterwards, a post-intervention assessment of all high-risk individuals will be conducted. **The primary outcome** is the net difference in post-intervention change from baseline in the proportion of high-risk patients treated with diuretics between intervention and control villages. A number of secondary outcomes including process and economic evaluations will also be conducted as well.

3.1. Sites

Gongbujiangda County and Linzhou County in the Tibet autonomous region located in southwest China have been selected as the study sites. The study sites fulfil the following criteria:

1) High CVD burdens: for example, previous study showed that the hypertension prevalence among adults 40 years and older in Yangbajing township in Dangxiong County, Tibet was as high as 59.6%[43].
2) Limited resource: there are usually only 1 or 2 PCPs at the township level serving a population of over 30,000 residents in a large geographical area. There are huge unmet needs for CVD prevention and management at the village level due to lack of trained CHWs.
3) Either having CHWs already in place or able to identify qualified candidates to be trained to fulfil the roles and responsibilities of CHWs.
4) Having certain governmental awareness and support to address CVD problems owing to previous program in these similar areas such as the Tibetan study described above[43], which helps to ensure the success of this pilot demonstration project proposed here.

3.2. Subjects

The targeted subjects for the baseline survey are all villagers aged 40 years old and above at the study sites. However, only high-risk individuals will be followed up during the intervention (if in the intervention group) and then assessed in the post-intervention survey (both intervention and control groups).The high-risk individuals have been defined as:

1) Age is equal or older than 40 years old **AND** the subject has a self-reported history of **ANY** of the following diseases:
    a. CVD **OR**
    b. Diabetes **OR**
    c. Stroke (including both Ischemic Stroke and Haemorrhagic Stroke) **OR**
    d. Measured blood pressure is equal or greater than 160mmHg at two different time points in the same day during the baseline survey.

3.3. Intervention and Control

We do not plan to impose any geographical restrictions on the selection of villages such as the sites not being adjacent to each other because we expect the risk of contamination to be small. The intervention, albeit highly simplified to suit local contexts, will be hard to imitate by those in the control villages. Village officials and opinion leaders should understand the significance of cardiovascular prevention and management for their villages, support the participation of their villages in the study, and have CHWs (or candidates) willing to take part in the study. Randomization will be stratified by county and township. For the entire study, there will be 12 intervention villages and 11 control villages.

Villages in the control group will continue their usual practices while villages in the intervention group will receive the following intervention lasting one year long.

The **simplified cardiovascular management intervention** will have the following features:

1) Target individuals at high risk for CVD for maximal cost-effectiveness;
2) Simplify guideline-based CVD prevention and management schemes to suit local situations, emphasizing the importance of patient identification, referral, regular follow-up and a *"2+2"model*: 2 therapeutic lifestyle recommendations (smoking cessation and salt reduction) plus prescription of 2 effective and low-cost drugs (aspirin and low-dose diuretics) when applicable. The CHWs who will be utilizing this simplified management scheme will be thoroughly trained and tested for competency on the indications, contraindications and side effects of the two drugs. CHWs will be trained to ask about and recognize contraindications such as allergy to aspirin, aspirin-like medicines or herbs, concurrent use of digitalis containing medications/herbs with a diuretic, etc.. In such cases, the medication in question will not be prescribed. CHWs will also be trained to ask about and recognize side effects to these medications and to have patients discontinue their use in the event of any serious adverse side effects. As such, individuals in the intervention group will all receive therapeutic lifestyle recommendations as applicable, but may be prescribed both, only one, or none of the two drugs as outlined in the simplified management scheme depending on each patient's medical situation.
3) Enhance the capacity of local CHWs in CVD prevention and management through systematic training;
4) Train the CHWs to complete case management records (**Appendix 1**) documenting each follow up visit for all high-risk individuals identified in the baseline survey;
5) Ensure the effectiveness of training through healthcare system strengthening that integrate township PCPs, EDS, performance feedback to CHWs and performance-based payment;
6) Be flexible and adaptive to incorporate insights gained from process evaluation and program implementation;
7) Enlist the help of government officials in implementing the management schemes; we do not anticipate any problems in obtaining such support owing to our rapport in working with them before.

3.4. Outcome Evaluation

The primary outcome will be the net differences between the changes in the proportion of high-risk individuals treated with low-dose diuretics pre-and-post intervention between intervention and control villages. This process indicator is chosen for its close association with the intervention scheme, effect on lowering high blood pressure, and its excellent power. A number of **secondary outcomes** will be evaluated, including:

- The net difference in mean post-intervention blood pressure changes of high-risk patients from baseline between intervention and control villages;
- The proportion of high-risk individuals aware of the harms of smoking and/or a high-salt diet;
- The proportion of high-risk individuals treated with aspirin;
- The proportion of high-risk individuals receiving 5 or more follow-up visits in a year;
- Hypertension awareness, treatment, and control rates.

Outcome assessments will be done in exactly the same way in every village, regardless of its assignment to intervention or control and will include a baseline screening and survey and a post-intervention follow-up survey. Before the intervention begins, a village-wide screening will be done to identify and measure high-risk individuals in all villages. Study personnel will assist village CHWs to screen for village residents meeting the definition of high risk through a short questionnaire including age, sex, disease history, and measurement of blood pressure. For all participants identified as high risk, a more detailed questionnaire will be administered including lifestyle, medical care, and costs as well as measurement of body height and weight and waist circumference. See **Appendix 2** for the complete questionnaire. Administration of the questionnaire and blood pressure measurements will be conducted according to standardized operating procedures. Butter tea samples from consenting villagers will also be collected (in each village, 5-10 bottles of 10ml of homemade butter tea will be collected from randomly selected consenting participant's homes) to be sent for laboratory analysis of salt content to more objectively evaluate a common source of

the villagers' salt intake. Comprehensive interviewer training materials will be prepared and detailed interviewer instruction programs will be completed prior to commencement of the evaluation surveys. Access to the study population will be flexible through either door-to-door surveys or convening study participants to a central location or a combination of both approaches. The goal is to identify as many patients with existing CVD as possible and at least enough other high-risk individuals to reach the minimal target of 800-1,000 in 23 villages in total. At the end of one year, a post-intervention assessment of all high-risk individuals identified at baseline will be conducted with administration of the same questionnaire and measurement of blood pressure, body height and weight.

3.5. Blood Pressure Monitor Calibration

The accuracy of the electronic blood pressure monitor measurement needs to be considered due to the geographic feature of the study sites: high altitude. The study sites have an average altitude of 3600±400 meters above sea level. The model of the blood pressure monitor that will be used in this study is the Omron HEM-7201; this model has been validated in the plains (conforms to the standards published by Association for the Advancement of Medical Instrumentation and British Hypertension Society) but not in high altitude areas. The validation and accuracy of adapting this instrument in high altitude areas remain unknown. The Omron HEM-7201's operation pressure is from 700hpa to 1060hpa, while the average pressure value at the study sites is 515±120hpa. This value is significantly lower than the instrument's standard operation pressure range. Therefore, this discrepancy could affect the accuracy of the blood pressure measurements done at the study sites.

In order to overcome this issue, we will validate and calibrate the selected blood pressure monitor model in both sea level and high altitude areas. We will adapt the validation procedure, the International Protocol revision 2010 for the validation of blood pressure measuring devices in adults, published by the European Society of Hypertension (ESH) to validate the instrument[49, 50]. This validation procedure is confined to adults equal to and above the age of 25 years, and does not make recommendations for special groups, such as children, pregnant women and the

elderly. 33 subjects will be selected for the validation at each site (sea level and high altitude) representing different blood pressure ranges (Low: SBP 90-129, DBP 40-79; Medium: SBP 130-160, DBP 80-100; High: SBP 161-180 DBP 101-130). The validation procedure consists of the following steps:

1) Observer training and assessment
2) Familiarization session
3) Validation measurements
4) Analysis
5) Reporting

Additional information from the participants will also be collected in the standardized forms provided by the protocol (**Appendix 3**), including the participant's date of birth, age, sex, use of antihypertensive medications and arm circumference.

3.6. Process and Economic Evaluation

Process evaluation[51] is an important part of this pilot study and will be conducted by trained researchers and in some cases by CHWs among key stakeholders (12 CHWs, 4 physicians, 60 patients and caregivers, 5 government officials, and 30 rural residents) in Tibet, China through semi-structured in-depth interviews and focus groups. The contents of these interviews and focus groups will be recorded, transcribed and analysed using a qualitative descriptive interpretive approach combining thematic content analysis and constant comparison methods[52-53] facilitated by *QSR NVIVO 8.0* data management software. Each transcript will be carefully read and re-read. A provisional coding scheme will be constructed based on emergent concepts derived from the data and the transcripts will be subsequently coded in an iterative manner using these codes with the addition of new ones as new data are encountered. Codes will be sorted into categories and the underlying meaning of the categories will be formulated and tabulated into themes.

Economic evaluation provides essential information to guide effective policy-making[51, 54-55]. Costs data will be collected to permit an assessment of the cost-effectiveness of the interventional program. Cost effectiveness will be assessed initially in terms of cost per 5% increase in diuretics prescription and per unit reduction

in blood pressure for high-risk patients. However, additional modeling[56] will be conducted to extrapolate these trial-based cost effectiveness findings into estimates of cost per life-years saved and cost per Disability Adjusted Life Years averted[57]. These estimates will be based on evidence from the literature of disease progression and long-term treatment effects. Sensitivity analyses will be conducted to assess uncertainty in study findings associated with variation in study parameters[58].

3.7. Statistical Power

Key underlying assumptions for this study are: there will be 12 interventions villages and 11 control villages with an estimated total of 800-1000 high-risk individuals identified from all the villages at baseline; an intra-cluster correlation coefficient (ICC) of 0.01 or 0.02[26,59]; and two-sided alpha=0.05. For the primary outcome, assuming the proportion of diuretics prescriptions in control villages is 20% (conservative as preliminary data shows it to be <10%), the power to detect a 10% difference is excellent (>90%), similarly high with an ICC of 0.02. Assuming a standard deviation of systolic blood pressure of 15 mmHg among these high-risk individuals (also conservative because this is a relatively homogeneous group), the power to detect a 3 mmHg net difference in this secondary outcome between the intervention and control group pre-post differences will be > 90% (drop to 77% if ICC = 0.02).

3.8. Analysis Plan

The primary analyses will be done by comparing the pre versus post differences in the 12 intervention townships with those in the 11 control townships[60-61]. Not only the point estimates but also estimates of variances will be reported as 95% confidence intervals. All analyses will be done according to the principle of intention to treat and take into account design and cluster effects[62]. As supplementary analyses, a multilevel modelling approach among intervention villages will be undertaken to better understand differences in treatment effect among clusters. Data from qualitative research (interviews and focus groups) will be analysed and reported accordingly with the aid of *NVIVO* software.

3.9. Ethics and Confidentiality

This study has been approved by Peking University Health Science Centre (PUHSC). Individual consent of participants in the survey will be done in the usual way. No individually identifiable information in the case management records will be collected or digitised by project personnel.

4. Project Operation and Management

4.1. Project Personnel

Project team consists of the team from The George Institute for Global Health, China in Beijing and the team from The Tibet University in Lhasa. In The George Institute for Global Health, China, Professor Lijing L. Yan is acting as the project Principle Investigator (PI). Dr. Maoyi Tian and Ms. Ruilai Li are appointed as the Research Fellows. Local PI (Dr. Zhong Liu) and local bilingual Project Coordinators (Mr. Danzeng Dunzhu, Mr. Luobu Zhandui, Mr. Baima Duoji, and Ms. Zha Sang) compose the team at Tibet University.

4.2. Personnel Training

A 'train the trainer' model will be adapted for the training purposes. There are two levels of training for both baseline survey and intervention. First level training is a systematic training, open to the project personnel in Tibet University delivered by the team in The George Institute for Global Health, China. Contents include the ethics training, project protocol (including both baseline survey and intervention), interviewing techniques, administrating questionnaire, survey instruments, etc.. Trainees will be assessed and examined. Second level training is delivered by the qualified trainees from the 1st level training to local interviewers, CHWs, etc. in the local language.

4.3. Timeline

Task	Start Time	Finish Time
PUHSC Ethics Application	October 2011	November 2011
Duke Ethics Application	November 2011	December 2011
Blood pressure monitor calibration	April 2012	May 2012

Baseline survey 1st level training	December 2011	December 2011
Baseline survey 2nd level training	December 2011	December 2011
Baseline survey – Gongbujiangda County	January 2012	January 2012
Baseline survey – Linzhou County	May 2012	June 2012
Intervention training (1st and 2nd level) – Gongbujiangda County	January 2012	January 2012
Intervention training (2nd level) – Linzhou County	June 2012	June 2012
Intervention – Gongbujiangda County	February 2012	February 2013
Intervention – Linzhou County	July 2012	July 2013
Post-intervention survey – Gongbujiangda County	March 2013	March 2013
Post-intervention survey – Linzhou County	August 2013	August 2013
Process evaluation	August 2012	November 2013
Results analysis	March 2013	November 2013
Writing and Publication	July 2013	December 2013

5. Potential Limitation and Challenges

The biggest challenge for a project conducted in resource-scarce settings lies in its feasibility. For example, it is possible that some CHWs, even after receiving systematic training and passing the examinations, may not be able to adhere to the management scheme well. A number of other factors such as patient adherence, cultural resistance to intake of western medicines, and system barriers may also affect the implementation of the interventional trial. On the other hand, many strategies and positive influences are in place to reduce the likelihood of these problems:

1) The choice of the local partners with established collaborations with the China COE;
2) Local sites receiving governmental support already;
3) The extensive experiences of the study team in the China COE, the developed country partners, and collaborating local organizations;
4) Process evaluation and adaptive intervention built in the program.

The potential limitation of the study is that we will not be able to detect which component of the simplified cardiovascular management scheme works well and which does not. However, the process evaluation, though cannot answer these questions directly, can provide some insight for future implementation and policy making.

6. Policy Impact

The project is timely because it addresses the burgeoning health issue of CVD in developing countries that have just begun to tackle chronic diseases nationwide and with such efforts lagging behind in remote areas. This project will complement and draw upon the experiences of several directly related programs in China and strong government support has been received at the local sites. The fact that China – with the largest population in the world - is involved in the study further lends to its generalizability and its potential to develop into larger-scale studies in the future. The intervention is designed with sustainability and scalability in mind, and if proven effective, has the potential to be adopted by local and national policy makers for promotion and implementation in other areas.

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