

China Rural Health Initiative

High cardiovascular risk management and salt reduction in rural villages in China: a factorial cluster-randomized controlled trial

PROTOCOL

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SYNOPSIS

Cardiovascular disease (CVD) is the leading cause of morbidity, mortality, and disability in both urban and rural China, with higher burdens in the North than in the South. There are well-established interventions that could 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. The **overall goal** of this study is to develop, implement and evaluate effective, low-cost, and sustainable interventions for CVD prevention and management suitable for widespread implementation in rural China.

The **specific aims** are to evaluate the effects of:

1. Implementing a simple low cost CVD prevention and control package, delivered by primary care providers, on the difference in village “weighted” mean blood pressure between baseline and follow-up.
2. Implementing a community-based salt reduction and health promotion program, delivered by community health educators, on mean sodium intake of village adults.

Study design: This project will be a large-scale, factorial, cluster-randomized, controlled trial conducted in the rural areas of 5 Northern Provinces. The study team has long-term collaborations with local academic institutions and governments in these provinces (Hebei, Liaoning, Ningxia, Shanxi, and Shaanxi). Two counties will be selected from each province. In each county, 12 townships will be invited to participate in the study with a projected total of 120 townships. The township (not the villages) has been selected as the unit of randomization because all village primary care providers in the same township are managed administratively and supported technically by the township healthcare center. One village in each township, the village most central to the geographic area covered by the township, will be included in the study. Randomization will be stratified by county in a factorial design. There will be 30 townships receiving both the primary health care package and the salt reduction interventions, 30 receiving package only, 30 salt reduction only, and 30 receiving neither interventions (usual care).

The “**primary health care package intervention**” will target individuals at high risk for CVD (physician-diagnosed history of coronary heart disease, ischemic stroke, or hemorrhagic stroke, or older age - 50 years or older for men; 60 years or older for women - and having physician-diagnosed diabetes mellitus or systolic blood pressure ≥ 160 mmHg). The specific elements of the intervention comprise: 1) technical training provided to village primary health care workers to screen, classify, and manage high-risk patients; 2) development of a simple case management record system within village clinics; 3) digitized central database and performance feedback to health workers; and 4) a performance-based economic incentive to health workers.

The “**community-based salt reduction and health promotion**” program will be delivered by community health educators and aim to reduce mean sodium intake. This intervention will be a multi-faceted program including general community health education, specific targeting of patients at high risk of blood pressure-related disease and a food supply measure designed to promote the sale of low-sodium salt through the village convenience stores.

All **outcome assessments** will be done in exactly the same way in every village, regardless of its assignment to intervention or control, by survey staff unaware of the randomized allocation of the villages. A baseline and a follow-up random sample survey (2 independent samples) will be conducted in all of the

120 villages. In each village, the survey will collect data from 40 consenting older adults (50+/60+), half men and half women. Blood pressure, weight, height and heart rate will be measured and recorded according to standardized protocol. A brief questionnaire will be administered by survey staff to collect information on disease history, medication use, care seeking patterns, and lifestyle factors. In addition, surveys of adults 20+ (20 persons per village) will be conducted with collection of 24-hour urine excretion to determine low-sodium salt use, among whom, 12 persons will be sampled from the 40 consenting older adults and 8 persons will be sampled from the village resident roll. The **primary outcomes** to assess the primary health care intervention will be the “weighted” mean blood pressure level between baseline and follow-up in the survey. The primary outcome to assess the salt reduction program will be average 24-hour urinary sodium excretion level. A number of secondary outcomes such as hypertension awareness, treatment, and control rates and mortality and morbidity measures will also be assessed. Process and economic evaluation will be conducted, if additional resources permit.

Time line: The two interventions will be implemented at two different stages with the package intervention starting first in the fall of 2010 and the salt reduction about 6 months later in the spring of 2011 due to practical concerns of the complexity of starting two interventions at the same time. The intervention will last for 2 years for the package arm and 1.5 years for the salt reduction arm with anticipated end time of Nov 2012.

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OVERALL GOAL, SPECIFIC AIMS AND HYPOTHESES

The **overall goal** of this study is to develop, implement and evaluate effective, low-cost, and sustainable interventions for cardiovascular disease prevention and management suitable for widespread implementation in rural China.

The **specific aims** are to evaluate the effects of:

3. Implementing a simple, low cost high cardiovascular risk management package (“package” hereafter) delivered by primary care providers (village doctors) with a focus on individuals at high risk of cardiovascular disease (“high-risk individuals” hereafter), on the difference in village “weighted” mean blood pressure between baseline and follow-up.
4. Implementing a community-based salt reduction and health promotion program delivered by community health educators on the average sodium intake level, as measured by 24-hour urinary sodium excretion.

The corresponding **null hypotheses** that will be tested are:

1. Implementing the package will not have “significant” impact upon the difference in village “weighted” mean blood pressure between baseline and follow-up.
2. Implementing the community-based salt reduction program will not have “significant” impact upon the average sodium intake level, as measured by 24-hour urinary sodium excretion.

It is worth noting that the null hypotheses are specified in a non-typical way to include “significant” impact in them. The rationale is that for this project with strong governmental support from its inception and potentially large policy implication if proven effective, we expect a larger than usual effect size for the results to be meaningful to policy makers and for widespread adoption in rural China. If the effect size is only scientifically, statistically or even clinically meaningful, it won’t be considered “effective” or an impact “significant” enough to support national policy decision making.

BACKGROUND AND SIGNIFICANCE

Cardiovascular disease is the leading cause of death in both developed and developing regions and the great majority of cardiovascular disease occurs in low and middle income countries.[1] In addition, about half of the deaths attributable to cardiovascular disease in developing countries occur below the age of 70 years, in contrast to about a quarter in developed countries. With no end to the rise in cardiovascular disease burden in developing countries in sight,[2] the identification of novel strategies that can address cardiovascular disease burden in developing countries is a global health priority.[3, 4]

BURDEN OF CARDIOVASCULAR DISEASE IN RURAL CHINA

Cardiovascular disease is the leading cause of death in China, responsible for about 3.5 million (38%) deaths in 2008.[1] By contrast to Western countries, stroke is much more prevalent and a greater cause of disease burden than coronary heart disease. There is also marked variation in the pattern of cardiovascular disease within China, with higher rates in Northern regions and lower rates in Southern regions.[5, 6] Reflecting the major contribution of cerebrovascular disease to the vascular disease burden in China, high blood pressure is the leading modifiable risk factor for cardiovascular disease[7] and its importance is greatest in rural and northern regions where salt consumption, high blood pressure and the incidence of stroke are both very high.

THE CHINESE RURAL POPULATION AND HEALTHCARE SYSTEM

The majority of the 1.2 billion Chinese population live in rural areas.[8] China has 33 provincial administrations including 283 cities and 2859 rural counties.[9] Each county is further divided into about 15 townships (average township population size = 20000) and each township, in turn, comprises between 10 and 20 villages (average village population size = 1500). The rural healthcare system has a 3-tiered structure that mirrors the broader administrative organization of rural China - at the county level there are county hospitals and county centers for disease prevention and control, at the township level there are township community healthcare centers, and finally beneath that the village clinics (or healthcare stations).[8] The village clinics are administered and receive technical support from the townships and the townships are, in turn, administered and supported by the county Bureau of Health, comprised of the county hospital and county centers for disease control. On average in rural China there are 1.2 health care workers per 1000 residents, with the village primary care providers comprising a substantial proportion.

In each village, there is usually at least one primary care provider, a licensed village doctor who typically has received a limited professional training after completing high school. Most of the village doctors have prescription rights for basic medicines on the national essential drug list. The village clinics, themselves, are typically one or two dedicated rooms although most will contain only very limited medical equipment. In some villages, the

village doctor is assisted by another healthcare worker, usually a woman, who has responsibility for maternal and child health and health education. The primary care providers and other healthcare workers live in the villages and work part-time with a modest salary provided by the county government; many work primarily in private practice although in some developed rural areas they may be full-time employees of the township government. Most consultations and subsequent care will require additional out-of-pocket payments by the patient to the primary care provider.

Each village also has an infrastructure that can be utilized to support community-level health promotion activities beyond the clinic setting. By training community health educators to address high salt intake and the potential value of salt substitute, and by developing educational tools and materials for this purpose, the salt reduction arm will make effective use of these communication channels for health promotion.

THE CONTROL OF BLOOD PRESSURE IN CHINA

In 2002, the prevalence of hypertension in China was broadly similar in rural (17%) and urban areas (21%),^[10] although awareness, treatment, and control rates were significantly lower outside of the cities (19%, 13%, and 3% vs. 30%, 24%, and 6% respectively).^[10] The gaps between these figures and those achieved in developed countries such as the US (66.5%, 53.7%, and 33.1% respectively in 2003-2004),^[11] serve to demonstrate both the lack of adequate intervention and the great potential for improvement in China. There is clear evidence that, for most individuals, blood pressure-related risk can be effectively managed by using low-cost drug treatments.^[12] Adopting a healthy lifestyle can also help individuals to control their blood pressure^[13] although adherence to the required dietary and behavioral changes is often poor and the real potential for these strategies lies in their population-wide application through centralized approaches to intervention.^[14]

China has established guidelines for the control of blood pressure that provide comprehensive guidance on diagnosis, management and monitoring.^[15] However, as is the situation for most countries, these guidelines are implemented incompletely in China and there is a need for the key messages to be disseminated more widely and adapted to different settings for not only better understanding of the guidelines but also better achievements of treatment goals in clinical practices especially in the primary care settings. Simplification and abbreviation is particularly important if blood pressure control is to be improved in rural areas where the primary care providers have only minimal training and limited access to resources.

Another reason for the review of existing hypertension guidelines is the need to ensure that the scarce resources available to rural areas are assigned as efficiently as possible. Accordingly, most guidelines for the prevention of blood pressure-related diseases in developed countries now incorporate absolute risk assessment as a key component of the process for deciding which individuals should be treated.^[16-18] The rationale for this approach is that the association between blood pressure and vascular risk is continuous, not

dichotomous, and the observation that blood pressure alone (unless it is very high) is a rather poor discriminator of risk. A series of studies have shown the much greater efficiency of allocating blood pressure lowering on the basis of an absolute risk assessment rather than a blood pressure measurement alone.[19, 20] This approach means that fewer patients can be treated, at lower cost, with more events averted because lower risk patients with borderline hypertension are not treated while high risk patients with 'normal' blood pressure are treated.

Since the Framingham risk prediction score does not fit the Chinese population, we used Chinese 10-year fatal and non-fatal ischemic cardiovascular disease risk prediction score to estimate the least risk for our defined high cardiovascular risk individuals.[21] According to these estimations, the 10-year risks are 7.0% for men aged 50-years old and 5.0% for women aged 60 years old who only had SBP \geq 160 mmHg but had no other risk factors such as smoking, overweight, high cholesterol and diabetes. Considering the high prevalence of those risk factors among the defined high risk population, the estimated 10-year absolute risk of ischemic cardiovascular disease would be at least 8-10% for individuals meeting our high-risk definition: either 1) having a disease history of coronary heart disease, ischemic or hemorrhagic stroke (of any age); or 2) meeting the age criteria (50 or over for men, 60 or over for women) and having SBP \geq 160 mmHg; or 3) meeting the age criteria (50 or over for men, 60 or over for women) and having diabetes.

CURRENT MANAGEMENT OF CARDIOVASCULAR DISEASE IN RURAL CHINA

At the village level, strategies for the control of cardiovascular disease are mostly absent. National clinical guidelines for the management of hypertension and cardiovascular disease are rarely disseminated to, or implemented by the village primary care providers. The financial system under which the system operates further mitigates against the uptake of routine preventive screening and care by the community.

Identified priority areas for cardiovascular disease control in rural areas are high blood pressure (driven by very high-salt intakes)[22-26] and smoking (particularly among men).[1, 10] Physical activity levels, by contrast, remain favorable compared to their urban counterparts, with many rural residents engaged in farm work. Another important consideration is that while rural-urban migration has been a dominant feature of recent Chinese demographic changes, most migrant workers that fall ill return to their country homes, where they often require long-term care. The currently very limited capacity of the medical personnel coupled with an increasing prevalence and morbidity caused by cardiovascular disease provides a strong rationale for intervention at both the clinical and population level.

DRUG-BASED INTERVENTIONS FOR CARDIOVASCULAR DISEASE PREVENTION

Results from large-scale randomized trials have identified a number of highly effective interventions for stroke prevention.[12] Blood pressure lowering regimes and anti-platelet

therapy,[27] in particular, are highly effective strategies for prevention amongst high-risk individuals. Furthermore, with the advent of widely available generic medicines, drug-based management can be afforded by the health systems and communities of even developing countries. The wider use of these therapies has great potential to reduce the morbidity, mortality, and economic burdens of cardiovascular disease in rural China.

SALT REDUCTION FOR CARDIOVASCULAR DISEASE PREVENTION

There is clear evidence from both observational studies[28] and overviews of randomised trials[29]·[30] that lower levels of salt consumption are associated with lower levels of blood pressure.[30, 31] Similarly clear are the beneficial effects of blood pressure lowering on major vascular events.[32-34] While the data directly linking salt reduction with mortality and morbidity benefits is more limited,[28, 35-39] the totality of evidence relating to the effects of salt on vascular disease is compelling. Most recently, the World Health Organisation has issued a technical report recommending that each of its member states implement a national salt reduction strategy for vascular disease prevention.[40]

Salt reduction has greater potential in rural China than almost anywhere else in the world. Very high levels of salt consumption,[41, 42] very little use of processed food and most dietary salt deriving from home cooking makes the removal of salt from the diet easier, cheaper and more worthwhile than in almost any other setting.[20] Interventions that jointly sought to educate the population about the harmful effects of salt and to decrease consumption levels,[43] in conjunction with efforts to make salt substitute[44] more widely available would be expected to have the greatest impact.

THE EFFECTS OF PRIMARY CARE PROVIDER TRAINING

Previous research on the effects of primary care provider training has been limited. It has been reported that special skills training could help rural physicians upgrade their skills and gain new competencies. In addition, physicians after the initial training are able to pursue more training opportunities on their own in the future and return to practice in their rural communities than in the past.[45] One small study conducted by our research group in rural China demonstrated that the hypertension control rate could be significantly improved when village doctors receive proper training on simplified clinical guidelines tailored to their level and educational background aided by certain management and support to village doctors (see the next section for more details). Some studies investigated both a provider-based approach and a patient-based approach and generally found that the combined approaches are more effective than physician training alone.[4, 46, 47] For example, a study conducted in rural Pakistan [46] showed that the multivariable reduction in systolic blood pressure was significantly greater in the combined intervention group (10.8 mmHg, 95% CI: 8.9 to 12.8 mmHg) than in the physician intervention, patient intervention, or control groups ($P<0.001$). These studies indicated that a combined intervention including physician intervention and patient intervention had bigger effects compared with one intervention alone. Therefore, in this trial, both a primary-care based intervention and a community-based intervention targeting high-risk individuals and other rural residents will

be evaluated.

PILOT WORK UNDER-PINNING THIS PROJECT

A Simplified Approach to Managing Cardiovascular Disease in Chinese Communities

In collaboration with colleagues in Canada we conducted a pilot study to evaluate a simplified approach to managing cardiovascular disease using two community health centers in Beijing (1 urban and 1 rural) and two centers in Baoding City, Hebei Province (1 urban and 1 rural). Both quantitative methods (chart review and questionnaire surveys of 50 patients in each center) and qualitative methods (participatory observation and focus groups with physicians and patients separately) were used. The baseline hypertension control rate was 29.3% in urban centers and 13.9% in rural centers. Use of anti-hypertensive medication (including traditional Chinese medicine) was similarly low in both rural (30.6%) and urban (30.2%) centers as was use of aspirin (36.9% vs. 31.4%). Rates of diuretic use were also very low (6.9% urban and 3.2% rural).

Development, promotion, and evaluation of “Practical guidelines for community-based hypertension prevention and control”

In 2001, the PI of the present study convened a national 50-member expert committee supported by the Chinese Cardiology Society, Beijing Hypertension Prevention and Control Committee, National Cardiovascular Prevention and Control Institute, WHO cardiovascular research and training collaborative center, and China CDC. On the basis of “Clinical guidelines for hypertension prevention and control in China,” a simplified practical yet evidence-based and validated guideline “The Practical Guidelines for Community-Based Hypertension Prevention and control” was developed by this expert committee through 12 group discussions and the Delphi method. The practical guideline was publicly released in October 2002 in Beijing at the Hypertension and Related Diseases Academic Conference. In 2003, the Bureau of Disease Prevention and Control in the China Ministry of Health approved the promotion of “The Practical Hypertension Prevention and control Guidelines for Grass-root Levels” nationwide. Within a year, over 10 provincial or municipal government agencies including CDC, Bureau of Health, primary care foundation, cardiovascular disease prevention and control office purchased the Guideline for widespread adoption; training classes were held successfully in 7 cities with about 1,800 trainees. The total number of primary care providers trained was over 30,000.

In 2004-5, to evaluate the effect of training village doctors for the practical guidelines, a one-year randomized intervention trial in 2 urban and 2 rural community health centers in Beijing (560 trial patients) showed dramatic improvements in many aspects such as hypertension control rate (26.4% control group vs. 77.9% intervention group in the 2 rural centers; 40.3% vs. 75.2% urban by the end of 12 months) (Table 1). During the intervention period, average pharmaceutical costs of hypertensive patients in urban areas in the intervention group was 569.4 yuan, significantly lower than the control group 766.5 yuan ($p < 0.05$); in rural areas, also lower but not statistically significant (295.6 vs. 354.1, $p > 0.05$).

Table 1 The hypertension control rates at follow-up

Control rate	Urban		Rural	
	Intervention	Control	Intervention	Control
3 months	49.4	45.8	35.1	18.4
6 months	64.3	50.9*	40.3	23.9*
9 months	70.4	52.1*	62.0	22.0**
12 months	75.2	40.3**	77.9	26.4**

vs. Intervention: * p<0.05; ** p<0.01

The feasibility of implementing a salt reduction program

In 1988, the PI of the present study conducted a small-scale trial to evaluate the feasibility and effect of implementing a salt reduction program in 16 households (38 villagers) in Hanzhong, Shaanxi Province. The results show that, the mean salt intake reduced to 6.1 ± 1.7 g/day from 11.1 ± 3.7 g/day, after 12-weeks intervention. Average reduction in daily salt intake was 5.0 g, of which 3.9 g/day came from reduced consumption of high-salt food such as preserved vegetables and beans. The urinary sodium and urinary sodium/potassium ratio from 8-hour nightly urinary excretion were all reduced; however, the reductions were not statistically significant. Compared with baseline, the reductions of SBP and DBP were 12.5mmHg and 7.8mmHg ($p < 0.01$ for both). These results demonstrate that simple, clear, and specific dietary instructions on salt reduction can effectively help rural residents reduce their salt intake. Unfortunately, no control group was included in this study.

In 2004-2005 we conducted, in rural China, a randomized trial including 608 high risk individuals recruited from 6 townships (and some 30 villages) in rural and suburban Northern China. Participants were assigned at random to receive either a low-sodium, high potassium salt substitute or continued normal salt. At completion of the 12 months of follow-up systolic blood pressure was 5.4mmHg (95% confidence interval 2.3 to 8.5) lower in the salt substitute group compared to the usual salt group, with evidence that the blood pressure reduction was increasing with time ($p = 0.001$, Figure 1). Adherence to the salt substitute was very high with 98% of participants reporting using the study salt/salt substitute for all or nearly all of their food preparation during the study period. Limited resources precluded the collection of 24hr urine samples and detailed dietary questionnaires but the sodium: potassium ratio estimated from spot urine samples fell as expected in the intervention group and there was no reported difference in the saltiness, flavour and

acceptability of foods between the participants randomized to salt substitute and those randomised to continued normal salt.

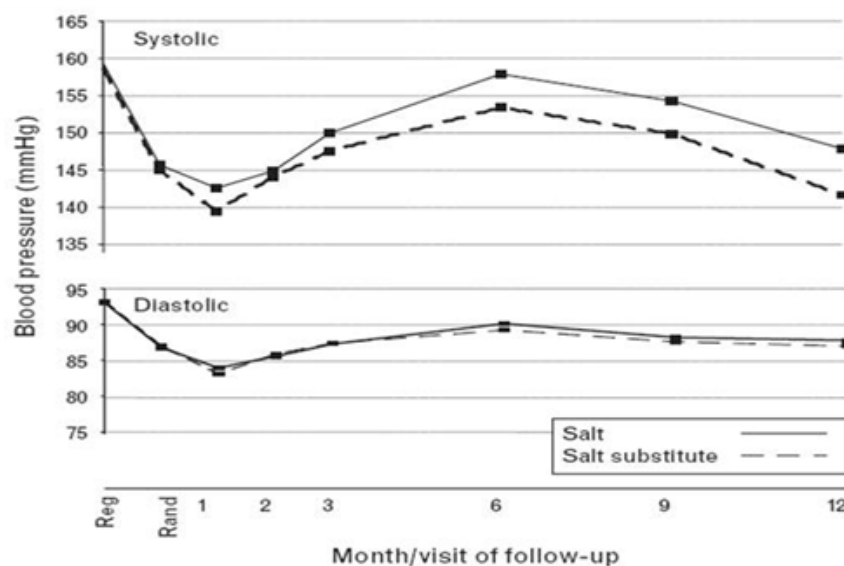


Figure 1 Mean systolic and diastolic blood pressure levels at each clinic visit by treatment group (mmHg).

We conducted another randomized double-blind controlled trial on salt substitute among 220 hypertensive patients and their 348 family members in rural Beijing from 2005-2006. After the one-year intervention, systolic blood pressure reduced by 4.1 (0.8, 7.4) mmHg (measured clinically), 3.1 (0.4, 5.8) mmHg (measured by home monitoring), and 2.4 (-2.4, 5.7) mmHg (ambulatory monitoring) respectively. Among family members, systolic BP by home monitoring reduced by 1.5 (-0.4, 3.4) mmHg, of which family members with hypertension had a reduction of 2.7 (-1.9, 7.2) mmHg and with normal blood pressure, only 0.5 (-1.2, 2.1) mmHg. Reduction in systolic BP was bigger with older age. Further analysis showed that withdrawal from medication was more pronounced in the salt substitute group than control group (normal salt), reaching statistical significance by the 3rd month ($p < 0.05$). During the trial, all (100%) people in the salt substitute group reported consuming the salt provided to them “all” or “most” of the time and 98.2% of the participants in the control group (normal salt) reported so. No between-group difference in compliance was detected ($p > 0.05$).

A similar 3-month randomized single-blind trial conducted in Tibet in 2009 among 284 hypertensive patients showed a bigger reduction [-8.8 mmHg (95% CI: -19.6 to -1.0) systolic and -4.5 mmHg (95% CI: -8.5 to -0.6) diastolic respectively] in this high-altitude area with very high prevalence of hypertension and higher average baseline blood pressure level.

There is currently significant interest in the potential for salt substitutes to decrease vascular disease in China and in Beijing there is a directive requiring greatly increased sales of salt substitute by the Beijing Salt Corporation. Against this background there is a high likelihood that it will be possible to make salt substitute more widely available in rural China

and this will be a core component of the salt reduction program.

SIGNIFICANCE OF THE PROPOSED STUDY

Rural China suffers an enormous burden of avoidable death and disability as a consequence of premature vascular disease.[48] There are very well established interventions that could avert much of this burden if the practicalities of how to deliver care to large numbers at low cost can be resolved. Examples of such interventions include blood pressure reduction, salt intake reduction, use of aspirin, and regular follow-up physician visits. What are not clear are the combined effects of these measures in resource-poor settings in rural China, and feasibility of widespread adoption. To obtain such evidence requires a local study done under the unique operational circumstances of rural China and within the resource constraints typical of this setting. The large-scale cluster-randomized controlled proposed here will precisely and reliably define the effect of two highly plausible intervention strategies on important clinical outcomes. The evidence provided by the project will form the basis for policy setting that has the potential to greatly reduce the occurrence of vascular disease in rural China and take an important step towards balancing the rural urban divide in health and healthcare.

STUDY DESIGN

This project will be a large-scale, factorial, cluster-randomized, controlled trial conducted in rural China with the township as the unit of investigation. The two main interventions to be evaluated are: 1) a primary-care based high cardiovascular risk management package delivered by village doctors; 2) a community-based salt reduction program delivered mainly by community health educators.

PROVINCES, TOWNSHIPS AND VILLAGES TO BE INCLUDED

The study will be done in 5 Northern Provinces utilizing established collaborations with local academic institutions and governments. The five provinces to be included are Hubei, Liaoning, Ningxia, Shanxi, and Shaanxi. The number of counties in the Provinces ranges from 8 (Ningxia) to 136 (Hebei) and the average number of townships in each county ranges from 12 to 22. These provinces are known to have high rates of vascular disease with a substantial burden caused by high blood pressure. [10]

Two counties will be selected from each Province on the basis of their willingness to participate in the project, their proximity to the local research team and their being broadly representative of the socioeconomic development level of the Province. In each county, 12 townships will be invited to participate in the study with a projected total of 120 townships. Selection of townships will be determined by a number of factors such as convenient transportation and preferences of the country bureau of health. It is important to note that the non-random selection of the counties and townships is not a significant issue for a research project of this design. The key is that assignment of townships to intervention and control conditions is by chance alone and this will be achieved by the randomization process.

All village primary care providers in the same township are managed administratively and supported technically (especially in public health and health education) by the township healthcare center where they regularly meet and receive training and supplies. A design that sought to deliver intervention and control to villages within the same township would be at high risk of contamination because of the township-based organizational structure for healthcare delivery. Therefore, township is chosen as the cluster.

Although the townships are the units for randomization, only 1 village from each township will be selected to participate in the study. In this way, the possible contaminations will be minimized best. The village to be selected should be as central as possible to the geographic area covered by the township, but should not be the Central Village where the township government and healthcare center locate, and the total population should be between 1000 to 2500. The reasons are to reduce the variance between villages, increase the balance between the intervention and control groups, and decrease the complexity and difficulties that we may have in implementing the intervention and evaluation during the study.

In the selection process, townships can not determine whether they will be in the intervention or control group, which will be governed by the randomization process only. However, if the primary care provider in the selected village declines to participate in the study, the next most geographically central village will be offered participation until a consenting village is found. Willingness to participate will be determined *before* the randomization process commences and villages will make the decision about whether or not to participate in full knowledge that they may be assigned to either intervention or control. Villages that decline to participate after randomization cannot be substituted with alternate villages since this would nullify the randomization process and introduce bias.

RANDOMIZATION

A stratified randomization will be used to assign the townships into 4 groups: high CVD risk management package only, salt reduction only, both package and salt reduction, and usual care (neither). Randomization will be stratified by county. In each county, the 12 townships will receive a random number and ranked according to the random number. Numbers 1, 5, 9 will be assigned to receive both interventions; number 2, 6, 10 to receive package only; 3, 7, 11 to receive salt reduction only; and the rest to receive neither intervention. For the entire study, there will be 60 townships with ‘package’ and 60 townships with ‘no package’ (with or without salt reduction) and 60 townships with ‘salt reduction’ and 60 townships with ‘no salt reduction’ (with or without “package intervention”). There will be 30 townships receiving both the package and the salt reduction interventions, 30 receiving package only, 30 salt reduction only, and 30 receiving neither interventions. All groups will receive the usual care.

INTERVENTION AND CONTROL

For the package intervention, the period of intervention will be 2 years; and for the salt reduction, approximately 1.5 years due to the staged onset of the two interventions.

‘Package’ intervention

The intervention package will be based upon the application of the core strategies described in the national practical guidelines for hypertension and cardiovascular disease management at grass-root levels in China, with further adaptation to ensure the interventions are feasible and affordable in rural China. Broadly the package will encourage the opportunistic identification of a set of high-risk individuals and then seek to improve their clinical management through the application of simplified guidelines and a defined follow-up schedule. The package will focus attention on patients considered at high cardiovascular risk on the basis of their falling into one of the following three groups, regardless of current medication use:

- Physician-diagnosed history of coronary heart disease, ischemic stroke, or hemorrhagic stroke, or
- Older age (50 years or older for men; 60 years or older for women – “50+/60+” hereafter) and having physician-diagnosed Type I or type II diabetes

- Older age (50+/60+) and SBP \geq 160 mmHg (note that for simplicity, DBP is not included in the criteria)

Details of the interventions are in [Appendix 1](#). Briefly,

- Implementing the CVD risk management package: Village doctors will screen, classify, treat, and follow-up high-risk cardiovascular patients according to the Package. A flow chart summarizing the main points and procedures will be designed as a wall poster and distributed to all doctors in the intervention group as an aid to help them adhere to the Package (see [Appendix 1-A](#)).
- Training on package: The training of the Package will be provided to all the participating village doctors in the intervention group. A cardiologist from each county hospital (10 in total) will be trained centrally in Beijing in both the package itself as well as how to be a trainer. The county hospital cardiologists will then train all village doctors in the intervention villages in their county. This “train the trainers” model is being used since it best emulates the practicalities of how the program might be rolled out if it would be proved effective. All village doctors can only begin intervention after they pass the training examination.
- The village doctors will also be trained and asked to complete a simple case management record (see [Appendix 1-B](#) for a sample record) documenting the initial clinical visit and each subsequent follow-up visit for all high-risk patients identified.
- Digitized central database and performance feedback: We will establish a central database and management system in Peking University Clinical Research Institute. An independent monitor will be appointed in each county to perform study quality control and to digitize all case management records every 2 months and upload the data via a secure network to the central database. Village doctors will be provided with regular semi-yearly performance feedback on key performance indicators (see [Appendix 1-C](#)) generated by the central database to reinforce their compliance to the package.
- Economic incentive: Observed performance will also determine the additional performance-based provider payments made to the village doctors with specific sums allocated for the achievement of specific clinical goals, especially preventive care that they are not normally compensated for such as blood pressure measurement, regular follow-up, lifestyle recommendations, and hypertension control (the last column of [Appendix 1-C](#) includes details on how the village doctors will be paid). The frequency of these payments will be the same as performance feedback – once in half a year.

‘Package’ control

Villages in the control group will continue their usual practices without the introduction of the ‘package’.

‘Salt reduction’ intervention

The salt reduction intervention will be a multi-faceted program including general community health education, specific targeting of patients at high risk of blood pressure-related disease and policy and environmental change (food supply) measures designed to promote the sale of salt

substitute through the village convenience stores. Broadly speaking this will be a community salt reduction campaign based upon the promotion of salt substitute.

The community-wide education component will seek to tap into the mechanisms already established in the villages for the dissemination of health information, such as township and village radio and TV broadcast system, public announcement system, bulletin boards in the village offices or village clinics, and promotional pamphlets. The community-wide education will be delivered directly by the community health educators with active engagement of the village council and the primary health care provider. The community health educators at the township and village level will be trained by county level public health experts. These county level staff will in turn be trained by central study staff under the same 'train the trainer' model used for the implementation for the 'package'. The community-wide education will include verbal counselling in small groups, public meetings, visual aids and other mechanisms throughout the two-year intervention period. Specific advice will be given to reduce the quantities of salt added to food during cooking, to limit the amount of salt pickled foods eaten, to soak salt cured meats in water overnight prior to eating them, and to purchase and consume low-sodium salt substitute instead of conventional salt.

The community-wide education will be delivered via universal knowledge dissemination by large educational slogans, and/or banner, and/or scrolls, and/or wall paintings in the village. In addition, posters and other educational materials will be prepared focusing on the most frequently eaten salty foods found in the study area promoting the use of salt substitute in their preparation. These materials will be prominently displayed in the village at the village council office, convenience stores and village bulletin boards. Supporting public lectures will be made by the community health educators with the organizational support of the village council.

The component of intervention targeting older (aged 50 plus) and high-risk individuals (with a self reported history of diabetes, high blood pressure, heart disease or cerebrovascular disease) will be delivered primarily by the village health care providers as part of an expanded chronic disease prevention role, with support from the village council and health educators. Healthcare providers will be trained to opportunistically screen adult patients presenting for any reason by asking simple questions about their ages, disease history, and making blood pressure measurements where possible. If a patient is identified as an older adult, or possibly falling into the high risk group they will be given particular encouragement to reduce salt intake and informed about the merits of replacing their salt supply with salt substitute. Community health educators may work alongside village doctors to hold special group counselling sessions or interactive events for high-risk patients.

Finally, there will be a concerted effort to make salt substitute available for sale in all village stores in the intervention areas. This will be a low-sodium, high-potassium salt-substitute (consisting of 65% sodium chloride, 25% potassium chloride and 10% magnesium sulphate) and the villagers will be encouraged to use the salt substitute to replace all household salt use (cooking, pickling and discretionary mealtime use). Salt substitute will be purchased initially by the study directly from the local salt company (in the counties or provincial salt companies if county salt companies do not

sell salt substitutes) at wholesale price and transported to village convenience stores. The salt substitute will be promoted by the village doctors, health educators and store keepers and the store keepers will sell the salt substitute at local market price making a small margin. The village store keepers will then purchase the next batch of salt substitute using the funds collected by selling the first batch. The village store keepers will only repay the initial costs of salt substitute to the study coordinator at wholesale price when the study intervention period is over. In this way the village store keepers will be able to stock the salt substitute at no commercial risk and the study will be required to outlay only a small initial sum to ensure salt substitute is available in all stores.

Consuming salt substitute by the general public has been considered as generally safe. The UK's Scientific Advisory Committee on Nutrition concluded that a potentially adverse reaction to a salt-substitute may occur following the ingestion of more than 17,600mg/day of potassium.[1] This would require the participant to ingest between 10-15 times their habitual daily intake of salt in the form of the salt substitute that we propose to use in this trial. Furthermore, a review of the published literature indicates that hyperkalemia, caused by ingestion of excess potassium in the form of salt substitutes, is rare and is quickly reversed upon cessation of the salt substitute.[2, 3] However, warnings will be given to villagers who have chronic renal disease that consuming large quantity of salt substitute might cause hyperkalemia and is not recommended.

Although salt substitute is a low-cost commodity that could be afforded by most rural residents, it is more expensive than normal salt. In order to determine the effect of subsidizing the price of the salt substitute on the use of salt substitute by village households, if sufficient funds are available, we will randomly assign 10 of the 60 clusters assigned to the active intervention to a price subsidization strategy which provides salt substitute for sale at the same price as salt. This will be achieved by providing the village storekeeper with a grant to enable the sale of salt substitute at a reduced price.

'Salt reduction' control

Villages in the control group will continue their usual practices without the introduction of any salt reduction initiatives.

OUTCOMES

The primary outcome for the package intervention will be the difference in village "weighted" mean blood pressure level between baseline and follow-up. In the calculation of mean blood pressure, all participants will be counted in the denominator. However, the weight (blood pressure level in the numerator) will be the actual measured blood pressure for patients who are not at target and zero for patients at or below target. For patients with existing diseases (coronary heart disease, stroke, or diabetes) is defined as measured systolic blood pressure < 140 mmHg; for patients without existing diseases, target is defined as measured systolic blood pressure < 160 mmHg. This

measure is designed in accordance with the definition of high-risk and the focus of the intervention on high-risk patients and to avoid potential biases resulting from only including high-risk patients (which can not be objectively identified post-intervention) in the outcome measure.

The primary outcome for the salt reduction intervention will be the difference in population mean 24-hour urinary sodium excretion between the aggregates of representative villagers in 60 intervention versus 60 control villages. Details for the outcome evaluation of salt reduction intervention can be found in Appendix 2 (China Rural Health Initiative Salt Reduction Intervention Outcome Evaluation Protocol).

Secondary outcomes for the package intervention

- The proportion of high-risk individuals in the village that are identified and regularly managed by the village doctors. Regular management is defined as visiting the village doctor at least once a month, at least 9 times in a year, and measuring blood pressure and prescribing cardiovascular medicine during each visit
- The proportion of high-risk individuals who had visited the village clinic and received pharmaceutical treatment from the village doctor at least once in the past year
- The proportion of high-risk individuals that are treated with a blood pressure lowering agent
- The proportion of high-risk individuals that are treated with aspirin
- The proportion of high-risk individuals that have systolic blood pressure controlled to less than 140mmHg
- The proportion of high-risk individuals that report having received therapeutic lifestyle changes recommendations from the village doctors
- The mean blood pressure level of older adults (50+/60+) in the village
- The proportion of older adults with hypertension (systolic blood pressure ≥ 140 mm Hg)

Secondary outcomes for the salt reduction intervention

- Mean 24-hour urinary potassium excretion.
- Mean ratio of 24-hour urinary sodium : potassium ratio.
- Mean systolic blood pressure
- Mean diastolic blood pressure
- Proportion of individuals with hypertension – defined as having a recorded SBP 140mmHg or above, recorded DBP 90mmHg or above, or currently on antihypertensive drug therapy
- Knowledge and practices relating to salt and salt substitute, including the proportion of individuals reporting efforts to reduce salt consumption and/or purchasing and using a salt substitute.

Exploratory outcomes

A series of exploratory outcomes will be assessed including fatal and non-fatal cardiovascular events and all-cause mortality.

OUTCOMES EVALUATION

All outcome assessments will be done in exactly the same way in every village, regardless of its assignment to intervention or control. Since blinding of data collection staff to the randomized allocation of the villages may be difficult to maintain there will be a strong focus on the training of staff in applying rigorously standardized evaluation techniques for every outcome that is assessed.

Comprehensive outcome evaluation for this study will include several components: some (baseline and end-of-intervention surveys and mortality/cardiovascular event surveillance system) can be used to evaluate both interventions, some (village doctor survey and case management records) pertaining to the package intervention only, and some others (24-hour urinary collection and salt substitute use and sales) pertaining to the salt reduction intervention only.

Baseline and end-of-intervention surveys (applicable to both interventions)

A baseline and a follow-up random sample survey (2 independent samples) of older adults (50+/60+) will be conducted in all of the 120 villages before and after the interventions. In each village, the survey will collect data from 40 consenting adults, half men and half women. Sampling will be done by the China International Center for Chronic Disease Prevention located in Beijing according to village rosters collected before the survey. All age-eligible (50+/60+) villagers will receive a random number. The random numbers will be ranked according to ascending order and informed consents will be sought according to the rank orders until 20 men and 20 women in each village consent to participate in the survey. Efforts to make sure that only one older adult from the same household will be recruited in the survey will be made – through a roster including household information or someone (e.g. village chief) who knows the villagers well enough to identify adults from the same household. Blood pressure, weight, height and heart rate will be measured and recorded according to standardized protocol. Blood pressure measurements will be made in duplicate with the participant seated after 5 minutes rest. Measurement will be recorded at least two minutes apart using an automated electronic sphygmomanometer according to standard procedures. A brief questionnaire (see [Appendix 3-A](#)) will be administered by survey staff to collect information on disease history, medication use, care seeking patterns, and lifestyle factors including knowledge and practices relating to salt and salt substitute. The end-of-intervention survey will be the same as the baseline survey except for a few additional questions relating to the consumption of salt and low sodium salt. All consenting adults will be asked to complete this end-of-intervention survey. (Appendix 3-B). Survey participants will receive a small gift valued at approximately 5 yuan (RMB) as a token of appreciation for their participation in the survey. Five yuan is approximately half of the minimal wage per hour for hourly workers.

High-risk patients in the evaluation surveys will be defined slightly differently from the high-risk definition in the package. It will be defined as having history of heart disease or stroke; or older age (50+/60+) and having diabetes; or older age (50+/60+) and having a measured systolic blood pressure ≥ 160 mmHg; or older age (50+/60+) and currently on anti-hypertension medication but having ever had a self-reported BP measurement ≥ 160 mmHg. See Appendix 3 for details on identification of high-risk patients from the random sample of older adults.

The outcome evaluation for the salt reduction intervention will also include other age groups to complete the survey questionnaire. Details of the participants is as follows:

Age group	Male (number of people)	Female (number of people)
20-29	1	1
30-39	1	1
40-49	1	1
50-59	2	2
60-69	5	5

Because the salt reduction intervention follow-up survey population of men (50 years and above) and women(60 years and above) will be sampled from the same population as the primary care provider (PCP) intervention follow-up survey, to save labor costs, in each village, 12 participant’s (male 50+, female 60+) taking part in the salt reduction intervention follow-up survey will be sampled from the 40 consenting adults who already attend the PCP follow-up survey. The remaining 8 younger participants will be randomly drawn from the village resident roll and consent from those 8 participants per village will be sought separately. Consent forms to be used at baseline and follow-up surveys are given in Appendix 4.

Because this is a cluster-randomized trial, it is not hard to outcome assessors to know the randomized allocation of the villages. However, standardized quality control procedures (such as independent reviews of the survey questionnaires and 10% audits) will be followed to ensure that survey personnel conduct the survey in an objective manner. Measurement of blood pressure will be done by an electronic device with recording functions to minimize the possibility of any tampering of the readings by study personnel. A systematic plan for quality control and assurance including the surveys and other components will be formulated and included in a separate document on the standard operation procedures for the study.

Additional end-of-intervention survey (applicable to salt reduction only)

An end-of-intervention survey of 12 individuals in the 6 strata will be conducted (not dependent on additional funding availability as the baseline survey) as it is crucial to have the post-intervention evaluation of these outcomes. If funding is available, high-risk individuals identified in the older adult surveys will also be receiving the 24-hour urine collection and household visits described below.

The baseline and follow-up salt assessment surveys will include 4 components, of which the first two are the same as the older adult survey described above and the latter two are for evaluating salt reduction intervention only:

- *Questionnaire* - For every individual a brief interviewer-administered questionnaire will be completed. The questionnaire will collect data on basic demographics, disease history, use of medications for blood pressure management and knowledge and practices related to salt.

- *Physical examination* - For every individual blood pressure, weight and height will be measured and recorded according to a standardized protocol.
- *24-hour urine collection* – All selected individuals will be provided with the materials required to collect a 24-hour urine sample and instructed how to do this. The subjects will be asked to discard urine voided at approximately 8.00 a.m. and to collect all urine voided during the subsequent full day until approximately 8.00 a.m. the next morning as a 24-hour urine specimen. The samples will be collected and the volume will be recorded. An aliquot of the sample will be taken and shipped to a central lab for assays of sodium, potassium, creatinine and microalbumin and the remainder will be discarded. In recognition of the onerous nature of the 24-hour sample collection process, participants that provide urine samples will be paid 25 yuan (RMB) to compensate them for their inconvenience. The completeness of collection will be assessed from the urine volume and from the subjects' reports and corrected by 24-hour urinary creatinine excretion level. The subjects whose average 24-hour urinary creatinine excretion level is below 85% or above 115% of predicted creatinine value will be excluded. [30] All participants who have been selected to fill out the questionnaire survey for the salt reduction intervention will also have a 24-hour urine collection. The urine samples will then be sent to a central laboratory in Beijing. Urine analysis for urinary sodium, potassium, creatinine and microalbumin will be done by a 'blinded' technician who is unaware of the intervention allocation of each participant. Before and during the transportation of the urine samples to the Beijing laboratory, the urine samples will be stored at - 20 ° C. More details are given in Appendix 2.
- *Dried blood spot* – Depending on availability of additional funding support, all participants will also have a small amount of blood drawn to measure glycosylated hemoglobin, blood glucose, blood lipids, creatinine etc. Collecting dried blood spots is a simple, minimally invasive way of collecting a blood sample from each participant, which involves gathering a few drops of blood from the finger on a filter paper (see Appendix 8 for protocol on finger prick blood collection). The collection and analysis of the dried blood spot will be done by well-trained survey personnel on site and in the lab. Samples will be stored and analyzed in a qualified laboratory with standardized quality control procedures after the approval by the institutional review board. Apart from the participant's ID code and initial, no other personal information will be shown on the samples. All analysis results will be kept confidential. Samples are frozen and stored in the laboratory for about 10 years, samples will be destroyed following on a standardized operation procedure.

Salt sales (applicable to salt reduction intervention only)

In all 120 villages, the convenience store owners will be asked to record total sales of salt (and salt substitute if sold in the store) in kgs and soy sauce in litres, and to report these data to the study staff each month.

Mortality and cardiovascular event surveillance system (applicable to both interventions)

A comprehensive surveillance system on all deaths and fatal and non-fatal cardiovascular events

will be established involving 3 main steps:

- 1) All village doctors including those in the control group will be required to record and report all deaths and fatal and non-fatal cardiovascular events. Non-fatal events will be collected using the modified WHO MONICA study protocol for acute coronary heart disease and stroke events.
- 2) All data on non-fatal, hospitalized, and fatal cardiovascular events from the county emergency and hospitalization records (including township healthcare centers if possible) and all deaths from the Public Security Bureau (and/or County Centers for Disease Control and Prevention) death registrations will be used to confirm diseases and causes of death, by study personnel.
- 3) All events will be reported to the central database in Beijing and be adjudicated by an independent adjudication committee.

This surveillance system will also provide a basis for data safety monitoring.

The details need to be found in the related file, the protocol of “Surveillance of all-cause deaths and major cardiovascular events among adults older than 25 years old”.

Case management records (applicable to “package” intervention only)

These records are an integral part of the cardiovascular disease prevention and control package in the management of high-risk patients in the 60 intervention villages. In addition, these records will also provide a large amount of clinical information for better evaluation of the effects of the intervention and better understanding of the mechanisms and processes through which the package exerts its impacts. Such understanding is crucial for future improvement of the package and its widespread adoption.

Trained project staff will conduct quality control and project monitoring to protect the rights and health of the participants in the package intervention and to ensure the accuracy, and authenticity of the CMR data. Monitoring methods will be fair, transparent, and corresponding to the code of ethics. Monitoring will be based on study protocol and include 3 parts:

- 1) the adherence of village doctors to intervention protocol: whether the Flow Chart are posted on the wall of the village clinic, whether the village doctor handbook is placed in an easily accessible location, and whether the patients in CMR are correctly identified according to the definition of high risk;
- 2) the authenticity of the patients in CMR: information in CMR will be checked against villager rosters to verify patient name, sex, age and address, and to confirm if the patient is real;
- 3) the accuracy of the CMR data: every 6 months, 5 patients will be randomly selected from all patients in the CMR database for each village. After obtaining informed consents, trained project staff will visit the patients, measure their blood pressure and heart rate, and ask them about their last visits to the village doctors, and pharmaceutical and non-pharmaceutical treatments provided by the doctors in the last 6 months. In addition, they will be asked to show the staff medications they are currently taking. Staff will record information on aspirin and diuretics including name, prescriber, length and frequency of use. The questionnaire is included in Appendix 5.

Village doctor survey (applicable to “package” intervention only)

In order to assess whether the village doctors in the intervention and control groups have comparable characteristics, we will collect basic information such as gender, date of birth, education, income, marital status, and years of clinical practice through a very short survey (see Appendix 6) for all the village doctors in the study. This survey will be conducted before the baseline village older adult survey but after obtaining their informed consent to participate in the study. In the case that they choose not to participate in the study even after group consent has been obtained from village leaders, we will select another village in the same township until we find consenting doctors and will conduct the village doctor survey in the consenting village. The village doctor survey will be conducted at baseline and at the end of the intervention period. The village clinic survey (see Appendix 7) will be conducted only at the end of the intervention period. The village doctor will be responsible for completing both of these questionnaires.

PROCESS EVALUATION

Aside from a comprehensive outcome evaluation, a process evaluation is also important.[49] If available resources permit, a process evaluation will also be conducted.[49] The information on how the program is performed can help the investigators to understand the extent to which the program is implemented as planned and explain the outcomes.[50]

- For the doctors in the “package” intervention program, an in-depth survey of specific questions related to the program implementation during and at the end of intervention will also be conducted.
- In the salt reduction intervention group, surveys during and at the end of intervention will be conducted among village doctors, village convenience store owners, and village heads about their effort in promoting the use of salt substitute and other salt reduction measures.
- For both the package and salt reduction interventions, interviews and focus groups at the end of the intervention will be conducted among key stakeholders involved in the programs including county officials, township health care center leaders, village doctors, community health educators, and villagers.

The details can be found in the related file, the protocols of “Interim Process Evaluation” and “Final Process Evaluation”.

ECONOMIC EVALUATION

An economic evaluation will be conducted to provide an assessment of the cost-effectiveness of each of the intervention strategies. The perspective to be adopted will be that of the health sector and will include:

- Costs to government in establishing and running the program including the costs associated with the provider financial incentives. These data will be extracted from financial statements from the project and partner organizations (e.g. hospitals and village clinics). Adjustment will be made to exclude protocol driven costs associated with conducting research
- Associated costs to individuals and government of medical treatment and medications and

the potential cost offsets associated with reductions in illness. Data on use of health care services and medications will be extracted from individual patient follow-up interviews. These resource items will be costed at standard prevailing market rates – recognizing variation in such unit costs across regions. Average costs per individual in each of the intervention groups will be estimated over the period of follow-up.

Cost effectiveness will be assessed initially in terms of cost per unit reduction in blood pressure for high-risk patients (package) or for older-adults (salt). However, additional modeling will be conducted to:

- Account for change in program costs associated with the scaling up of the intervention e.g. economies of scale through rationalization of upfront costs
- Extrapolate these trial based cost effectiveness findings into estimates of cost per life year saved and cost per Disability Adjusted Life Year (DALY) averted. These estimates will be based on evidence from the literature of disease progression and long term treatment effects.

These findings will enable the cost-effectiveness of the interventions tested in this study to be benchmarked against standard criteria such as that of the World Health Organization of a cost per DALY averted of less than three times gross national income.[51] Sensitivity analyses will be conducted to assess uncertainty in study findings associated with variation in study parameters.

STATISTICAL POWER

The sample size has been estimated to provide good statistical power (two-sided $\alpha=0.05$, $\beta=0.80$) to detect plausible effects of each intervention. Common assumptions of both sets of power calculations are: 120 clusters, equal randomization between intervention and control and an intra-cluster correlation coefficient of 0.05. These power calculations also assume that there is no interaction between the effects of the package and the effects of salt reduction.

- For the detection of the effects of the package, it is assumed that an average of 15% (with a variance of 0.01 around this average) will be identified as high risk individuals from the 40 survey participants in each cluster, a total of 960 high-risk patients in 120 clusters. It is also assumed that 50% of these identified individuals will be above target blood pressure of 140 at baseline and that 10% of the remaining 85% of individuals in the cluster will be above their target blood pressure of 160 at baseline. Assuming a standard deviation of systolic blood pressure of 12 mmHg for those with existing disease and 15 mmHg for those without, the power to detect various combinations of decreases (average differences in weighted mean blood pressure between baseline and follow-up) for these two groups was calculated. Specifically, at least 80% power is attained for a decrease of a 5.0 mmHg in those with existing disease and 2.0 mmHg for those without existing disease versus no decrease among control villages. This 5 mmHg difference corresponds to the reduction in systolic blood pressure for

those above the threshold of 140 mmHg. Previous clinical trials demonstrated that even just single drug treatment can lower systolic blood pressure by at least 10 mmHg on average, our targeted blood pressure lowering strategy in package intervention should produce even larger effect. In addition, our CSSS study showed that a low sodium salt substitute could reduce systolic blood pressure by 5.4 mmHg on average. We have reasons to believe that an effect equal or even larger than 5 mmHg systolic blood pressure difference is highly achievable. On the other hand, to achieve a difference smaller than 5 mmHg in systolic blood pressure among those actively managed is not considered meaningful in terms of policy implications. In other words, a smaller effect size is usually not regarded by policy makers as convincing enough for national policies.

- For the primary outcome of urinary sodium excretion, with 20 participants randomly selected from each village there will be 90% power to detect a 11mmol/day sodium (0.65g/day salt) difference in 24-hour excretion between intervention and control clusters assuming a standard deviation of 24hr sodium excretion of 60mmol/day.[32] An effect size of this magnitude would be anticipated to lead to important reductions in mean population blood pressure levels and to avert large numbers of events nationwide.

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Since no reliable prior data exist to provide estimates of the effect sizes for the salt reduction intervention, power analysis is done for several main secondary outcomes as well.

It is expected that there may be an interaction between the two interventions under investigation in this factorial trial. The power estimates described above are based on their being no interaction and are considered to be conservative since it is believed an interaction would be likely to increase rather than decrease the size of the effect achieved for either intervention alone. The reasons for this assumption are the known additive effects of different blood pressure lowering modalities and the likely high average blood pressure level of participants (will be well above the lowest plausible physiological blood pressure level). As such, it is considered unlikely that the joint effects of the interventions could achieve a ‘ceiling effect’ whereby the size of the blood pressure reduction is limited by the lowest physiologically achievable blood pressure having been reached. Both drug therapy and salt reduction are relatively weak interventions that are individually (or jointly) unlikely to reduce blood to a level below which it cannot be further reduced.

ANALYSIS PLAN

The primary analyses will be comparing the 60 pre versus post differences in the intervention townships with those in the control townships, separately for each intervention. For the package intervention, because these differences eliminate the cluster effect and can be assumed to be independent, a simple two-sample t-test will be used for the hypothesis testing. Not only the point estimates but also estimates of variances will be reported as 95% confidence intervals. We

will compare the post-intervention differences in the outcomes between the intervention group and the control group. In addition, we will also evaluate the differences between pre-and-post intervention levels for both the intervention and control group to see if the net differences between the 2 groups are statistically significant.

All analyses will include adjustment for the clustering effect and will be done according to the principle of intention to treat.

As supplemental analysis, a multilevel modeling approach will be undertaken to better understand differences in treatment effect among clusters. Townships will be considered as random effects and fixed effects will include age, sex, education, and lifestyle factors. In additional analysis, baseline blood pressure will also be adjusted.

DATA MONITORING AND SAFETY

A data and safety monitoring board is not considered necessary since all the interventions in the Package are based on current international guidelines and have been proven to be both effective and safe. The salt substitute and low salt diet have also been shown by our own or other's previous studies as effective and safe.

A data safety and monitoring plan will be established. The safety of study participants will mainly be assured by having expert consultation available to the village doctors and by monitoring digitized case management records. Village doctors will receive clear instructions to refer patients to hospital-based doctors or specialists, whenever necessary. Both emergency and non-emergency referrals are included in the training. The county cardiologist who will train the village doctors will be available for consultation should such needs arise. The case management records taken by the village doctors in the intervention villages will be digitized and uploaded to a central database on a bi-monthly interval. These records will be regularly reviewed by study cardiologists to detect any abnormal patterns including adverse effects and medically appropriate actions will be taken when necessary.

PROJECT TIMELINE

The two interventions will be implemented at two different stages with the package intervention starting first according to the following schedule and the salt reduction about 6 months later due to practical concerns of the complexity of starting two interventions at the same time.

- May 2010 - July 2010: ethics Committee submissions and approvals
- May 2010 – August 2010: development of standard operating procedures
- September 2010 –October 2010: baseline surveys and training the trainers (April-May 2011)

for salt reduction)

- October 2010 – October 2012: intervention; (since April 2011 for salt reduction)
- October 2012 to November 2012: follow-up surveys
- December 2012: study close-out and final evaluation survey
- January 2013 – May 2014: data cleaning, analysis, and report writing

ETHICS REVIEW AND HUMAN SUBJECT PROTECTION

Because of some overlap between the package and sodium reduction interventions, as they intersect at the level of the village doctor, information presented in this section pertains to all aspects of ethics review and human subject protection.

The project will be reviewed by the Ethics Committee of the Peking University Health Science Center in Beijing, China and the Duke University Health System Institutional Review Board, USA. Ethic review will also be conducted by the National Heart, Lung, and Blood Institute, USA.

Human subject protection certification and training

All collaborating organizations have received the FWA (Federal-Wide Assurance) from the US Department of Health and Human Services Office of Human Research Protections. All study personnel have received or will receive either on-line or in-person trainings on human subject protections and obtain the CITI certificate before they begin the study.

Participant informed consent

Participant consent for this project has particular challenges because of the community level nature of the intervention and the requirement to obtain community consent in addition to the usual individual consent.

Cluster level consent will be obtained through a consultation process involving the townships and villages. Government and community leaders from each will have the project explained to them including the process of random assignment of communities to the intervention and control conditions and the nature of the interventions. The study team will work with our local collaborators to first introduce the study to the provincial bureau of health. After obtaining their support and consent, we will introduce the study to the county department of health to seek their support and input on the selection of townships in their county to participate in the study. The consent process at each level will be similar: First, an initial group presentation and discussion of the project will be conducted. This will be followed by time for reflection and the opportunity for each stakeholder group to consult with the research team individually as required. A final decision to participate, or not, will be made at a second face-to-face meeting of the parties with the final decision provided to the researchers in writing at the county levels.

Individual consent of participants in the surveys will be done in the usual way. Individuals will be

free to participate or not as they see fit. Participant information sheet and consent form for the village doctors are in Appendix 5-A; for survey participants in Appendix 5-B, and for CMR quality control visit in Appendix 5-C.

There will be an estimated 10,000 high-risk patients to be managed in 2 years in 60 villages. No individually identifiable information in the case management records will be collected or digitized by study personnel. Only the first page of the case management records has individually identifiable information. Such information will be entered by the village doctors and can be viewable by only the village doctors and the study monitor digitizing such paper-based data. All high-risk patients in the package intervention group will be identified by a unique study ID. Patient records transmitted to the Data Management Centre will be identified only by a unique number and date of birth; in other words, no individually identifiable information such as name, address, or personal ID will be included in the digitized database. Therefore, there is no need to obtain informed consents from high-risk patients being managed by the village doctors as part of their enhanced clinical practices.

Participant risks and benefits

Two types of interventions are proposed: package and salt reduction. No or minimal risks will be imposed by the community education intervention (using means of public announcement system, flyers, and town hall meetings etc.) or by usual care planned for the control group. The package intervention will follow standardized guidelines for the identification and treatment of patients with high cardiovascular risks such as hypertension and cardiovascular diseases. These drugs (such as diuretics and aspirin) have been used in the market for many years and have been proven to be safe in most patients. Adequate trainings will be provided to the village doctors who prescribe these drugs. Outcome assessments will involve a simple set of questions, basic anthropometry, a blood pressure measurement and a 24hr urine collection. No or minimal risks will be imposed by these measurements.

A potential risk to the participant is the inadvertent release of his/her information obtained during the course of the study. This possibility is minimized by having computer-readable data records for statistical analyses identified only by code number and maintaining names, addresses, and other identifying information used in the study (when such information is collected such as in the surveys) in separate databases on secure servers with password protection. Paper records and other identifying information are maintained separately in locked files and all project personnel (including the data management team) will sign data confidentiality agreement and will be thoroughly indoctrinated in maintaining confidentiality of data. All data collected in this study will be kept strictly confidential with access granted to only authorized personnel. No report or manuscript will contain any information that would allow an individual participant in the study to be identified.

Benefits to individual participants include opportunity to have current cardiovascular risk factors evaluated at no cost, and treatments when needed for the package intervention group, and free education for the community education group. More importantly, results of the proposed study,

with small or no risk to individual participants, may have important implications for public health policy and allocation of resources for chronic disease prevention and control in rural China, where low-cost, effective, and sustainable strategies are urgently needed. Thus, potential problems in this research are few, low order, and potential benefits very great.

Inclusion of women, minorities, and children

There will be equal efforts to enroll men and women; thus by design the survey sample will be drawn to include approximately 50% women. The study will be conducted in 5 regions in Northern China where our 5 local partners are located. One of the regions is in Ningxia Hui People Autonomous Region where a lot of Hui minority people reside. More than 30% of the participants in this region, over 6% of overall sample, will belong to the Hui minority group. There are very few minorities living in the other 4 regions and will result in only small numbers of minorities being recruited into the sample there. The participants in the project will primarily be adults since it is adults that mostly suffer from hypertension and chronic diseases; hence, the topic is not relevant to children and none are to be included. However, the community education intervention aimed at all villagers in the same village may benefit children as well.

Amendments and additional submissions

Amendments to the protocol, participant information sheet or consent form will be submitted to the ethics committee for approval. Such amendments will only be implemented once ethical approval has been obtained, unless an amendment is being made to eliminate immediate hazards to study participants, which is highly unlikely in this study.

PUBLIC HEALTH SIGNIFICANCE

Vascular diseases are a large and rapidly growing cause of disease burden in China.[1] While some preventive care is available much of the population has limited access to chronic disease services and little capacity to pay for them. This is particularly true of rural areas where the majority of the Chinese population currently lives. The worsening circumstance of poor rural Chinese is a major national concern and strategies to enhance rural development are a specific focus of the National Reform and Development Committee, and combating rural-urban inequalities is at the core of China's most recent 5-year plan. Low-cost strategies for the improvement of health in rural areas are urgently sought and extensive consultations with researchers, ministry officials and industry indicate that strengthening the evidence base along the lines described here in this protocol would achieve significant support for policy change.

We expect the approaches being evaluated here would be highly cost effective.[21] The package intervention has its inherent costs in training, implementation, providing performance feedback and performance-based incentives; however, the whole package has been designed with the goal of scalability and sustainability. Formal economic evaluation will prove if this intervention will be cost-effective. While the salt substitute is more expensive than normal salt, it remains a very low

cost commodity that could be afforded by most. Population approaches to salt reduction have been identified by the World Health Organization as amongst the most cost-effective possible strategies for vascular disease prevention in developed and developing countries alike. [1]

The work proposed here will provide evidence about the practicalities and potential public health impact of the two interventional programs; in particular, how these interventions could, with appropriate government, industry and regulatory support, be rapidly implemented, with large health gains in rural China.

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APPENDICES

Appendix 1: Detailed Description of the CVD Prevention and Management Package

Appendix 1-A: Flow Chart to Identify, Manage, and Follow-up High-Risk Patients

Appendix 1-B: Case Management Record

Appendix 1-C: Key Performance Indicators and Payment Schemes

Appendix 2: China Rural Health Initiative Salt Reduction Intervention Outcome Evaluation Protocol

Appendix 3: Questionnaire

Appendix 3-A: Questionnaire for Baseline Population Survey

Appendix 3-B: Questionnaire for Follow-up Population Survey

Appendix 4: Participant Information Sheet and Consent Form

Appendix 4-A: Participant Information Sheet and Consent Form to be used for village doctors

Appendix 4-B: Participant Information Sheet and Consent Form to be used at time of baseline population survey and interview

Appendix 4-C: Participant Information Sheet and Consent Form to be used at time of follow-up population survey and interview

Appendix 4-D: Participant Information Sheet and Consent Form to be used for Case Management Record Quality Control

Appendix 5: Questionnaire for Case Management Record Quality Control

Appendix 6: Questionnaire for village doctors

Appendix 7: Questionnaire for village clinics

Appendix 8: Finger stick blood collection protocol

Appendix 9: Interim process evaluation protocol

Appendix 9-A: Village Doctor Questionnaire

Appendix 9-B: Interview Guidelines

Appendix 9-C: Participatory Observation Form

Appendix 9-D: Consent Form

Appendix 10: Final process evaluation protocol

Appendix 10-A: Interview Guidelines

Appendix 10-B: Participatory Observation Form

Appendix 10-C: Consent Form