

# SIMPLIFIED CARDIOVASCULAR MANAGEMENT (SimCard)

## STUDY

### A Cluster-Randomized Trial to Evaluate the Effects of a Simplified Cardiovascular Management Program in China and India

#### RESEARCH PROTOCOL

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## LIST OF ACRONYMS

China CoE: Center of Excellence- China International Center for Chronic Disease Prevention, Beijing

CHW: Community Healthcare Worker

CoE: Center of Excellence

CoE-CARRS: Center of Excellence in Cardiometabolic Risk Reduction in South Asia, Public Health

Foundation of India

CRFs: Case Report Forms

CVD: Cardiovascular Disease

EDS: Electronic Decision Support

EHR: Electronic Health Records

ICC: Intra-cluster correlation coefficient

PCP: Primary Health Center Physician

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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 well-established interventions such as lifestyle modifications and appropriate prescriptions and consistent use of aspirin and calcium channel blockers 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 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), on the proportion of patients appropriately treated with calcium channel blockers as well as a number of secondary outcomes. The main features of the **simplified cardiovascular management program** include: 1) focus on high-risk 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.

Building on our prior experiences, the George Institute for Global Health, China in collaborations with the Public Health Foundation of India with cross-fertilization of ideas and expertise proposes to conduct a **cluster-randomized controlled interventional pilot trial** in the rural areas in Tibet, China and Haryana, India. In each country, villages will be selected to be randomized to receive the intervention or usual care. Before the intervention begins, a village-wide screening will be done to identify and measure high-risk individuals in all villages. The intervention will be one year long. A post-intervention assessment of all high-risk individuals will also be conducted. Process evaluation, economic evaluation, and verbal autopsy represent important aspects of the evaluation matrix. The results of the study are expected to both advance scientific knowledge to prepare for future large-

scale studies and to provide translational evidence necessary for sound policy making to address the CVD problem in resource-scarce settings.

## STUDY OBJECTIVES

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 health care centers or community healthcare workers (CHWs), on the proportion of patients appropriately treated with calcium channel blockers as well as a number of secondary outcomes in resource-scarce settings in rural China and India

## BACKGROUND AND RATIONALE

Cardiovascular disease (CVD) is the leading cause of morbidity, mortality, and disability in not only developed but also developing nations. There are well-established interventions such as lifestyle modifications and appropriate prescriptions and consistent use of aspirin and calcium channel blockers 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. One particularly cost-effective approach for secondary prevention of CVD is to identify and manage individuals at high cardiovascular risk in order to prevent or delay events. This approach has been tested in the Rural Andhra Pradesh Cardiovascular Prevention Study (2007-2010) 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 will be more resources to do so.

**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 and existing programs evaluating how to translate scientific evidence into effective CVD management in relatively resource-poor settings at 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 mostly from developed countries. Whether the cost-effectiveness holds true in resource-scarce areas in developing countries and the practicality of how to implement these measures remain to be tested. Fourth and finally, we aim to improve CVD prevention and management through strengthening the healthcare system by integrating and developing the capacity of Primary Health Center Physicians (PCPs) and CHWs via training, Electronic Decision Support (EDS), performance feedback, and performance-based payment. These measures are designed to be both cost-effective and scalable in the future through translation to health policies.

## **SIGNIFICANCE AND PUBLIC HEALTH IMPACT**

**Significance** – Many regions in developing countries are now characterized as having triple burdens of the longstanding problems of infectious diseases, the rapidly rising burden of non-communicable chronic diseases, and the serious lack of economic and healthcare resources and a weak healthcare system incapable of dealing with these widespread health problems. While evidence-based national and international guidelines on managing chronic conditions such as hypertension, coronary heart disease, and stroke are well-established, cost-effective approaches suitable for adoption in triple-



burden areas in developing countries are not adequately investigated or well understood. This study aims to address the highly prevalent problem of CVD in the remote and poor areas that has not received much attention so far. The interventional model is designed to overcome inherent barriers in 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. 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.

**Public health impact** – High-risk approach is one of the two commonly used methods for addressing public health problems. Due to high prevalence of CVD, high event and fatality rates of CVD patients, and the large resulting 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 resources available to address it. Though not a population-wide approach, the high prevalence of high-risk persons in these places means that the interventions have the power to improve the health of large numbers of people in interventional areas. Given the enormous needs to prevent CVD in many poor countries and regions around the globe, 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.

## **WORK THAT LED TO THE PRESENT PROJECT**

The flagship project of the China International Center for Chronic Disease Prevention (**China CoE**) is the China Rural Health Initiative. This is a factorial cluster-randomized controlled trial evaluating two interventions for CVD prevention and management in the rural areas of 5 Northern provinces in China. The two interventions represent a high-risk based approach involving delivery of simplified guideline-based care to patients with high cardiovascular risks by village doctors and a population-based approach to promote low salt intake through health education and making low-sodium salt available in village convenience stores. The experiences gained from it will prove valuable for the

proposed project, which adopts a high-risk approach only with further simplification (and new measures not used in the current project) to meet local contexts with more scarce resources and lower capacity in general.

In 2009, the China CoE has worked closely with collaborators in **Tibet** on a series of studies in this high-altitude area with extremely limited healthcare resources: 1) a validation study demonstrating the usability of electronic blood pressure meters in high-altitude areas 2) a prevalence survey in Yangbajing Township in Dangxing County showing very high prevalence of hypertension in this area, 3) an interventional trial evaluating the effects of low-sodium salt (65% sodium, 25% potassium, 10% magnesium) and low-dose diuretics on blood pressure among 284 hypertensive patients in Dangxiong County. Impressed by the results of the study, the Tibetan government has charged the China CoE with the tasks of developing region-wide programs for CVD and hypertension control.

In collaboration with the Public Health Foundation of India (**CoE-CARRS**) and other partners, the George Institute for Global Health in India has conducted a Rural Andhra Pradesh Cardiovascular Prevention Study, also a factorial cluster-randomized trial involving 40 villages in the area. Besides a health promotion component promoting tobacco cessation, heart-healthy eating and physical activity, the algorithm-based care component involves training physicians or CHWs to opportunistically screen for people with existing heart disease, stroke or angina and offer referrals and behavioral modification recommendations to patients identified. The proposed study builds on the success of working with CHWs in rural Andhra Pradesh but extends the algorithm beyond identification to focus on management of high-risk patients and investigates innovative interventions not evaluated before such as EDS.

This project will promote global leadership and enhance research capacity through innovative research led from developing country centers seeking to improve the health of vulnerable and disadvantaged individuals. The project will be led by the China and India (New Delhi) Centers of Excellence (COEs) – two centers located in the two most populous countries in the world.

Investigators in both centers have prior experiences in this field that will ensure the success of the proposed project. In addition, working on this joint project will establish new research collaborations and cross-fertilizations of expertise with the potential to lead to other larger endeavors in the future.

## STUDY DESIGN

This project will be a cluster-randomized controlled interventional trial conducted in the rural areas in China and India as a large pilot study. In each country, villages will be selected to be randomized to receive the intervention or usual care. The main intervention is a simplified cardiovascular management program for high-risk individuals delivered by village CHWs with support of Primary Health Center Physicians (PCPs). Each country will follow identical standardized operating procedures to train research personnel, implement and monitor the interventions, and assess study outcomes. 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 and measure high-risk individuals in all villages. A post-intervention assessment of all high-risk individuals will also be conducted. The primary outcome is the net difference in post-intervention changes from baseline in the proportion of high-risk patients treated with calcium channel blockers between intervention and control villages. A number of secondary outcomes including process and economic evaluations will also be included.

## INTERVENTION AND CONTROL

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 calcium channel blockers); 3) enhance the capacity of local CHWs in CVD prevention and management through systematic training; 4) ensure the effectiveness of training through healthcare system strengthening that integrate township PCPs, EDS, performance feedback to CHWs and performance-based payment; 5) being flexible and adaptive to incorporate insights gained from process evaluation and program implementation; and 6) enlist the help of government officials in implementing the management schemes; we do not anticipate any problem in obtaining such support owing to our rapport in working with them before.

## OUTCOME EVALUATION

**The primary outcome** will be the net differences between the changes in the proportion of high-risk individuals treated with calcium channel blockers, 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 or 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 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 hospitalization and event history in the past year. Blood pressure and body height and weight measurements will be done for all older adults 40+ and those with existing diseases. Administering of questionnaire and blood pressure measurement will be conducted according to standardized operating procedures. 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 and other high-risk individuals. 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.

**Verbal autopsy** as an alternative method to verify causes of death to traditional hospital-based surveillance has been shown to be a feasible and valid approach in many developing countries. Our developed country partners have extensive experiences in this area. However, no study has been done in Tibet, China or Haryana, India, where reliable causes of death data are not available. To prepare for a large study with mortality as an outcome, we propose to include training on how to conduct verbal autopsy among the next of kins of the deceased in the training of CHWs. Because the validity of the method has been shown in previous studies and this component is included to test for feasibility of using CHWs to conduct verbal autopsy in the study regions only, no physician or hospital-based classifications will be done. A computer-based symptom pattern method will be used to classify causes of deaths. Since we will not have power nor do we plan to use mortality as study outcomes, verbal autopsy will not be conducted in control villages.

## **PROCESS AND ECONOMIC EVALUATION**

**Process evaluation** is an important part of this pilot study and will be conducted by trained researchers and in some cases by CHWs among key stakeholders (6 CHWs, 3 physicians, 60 patients and caregivers, 5 government officials, and 30 rural residents) in China and India through semi-structured in-depth interviews and focus groups. The contents of the these interviews and focus

groups will be recorded, transcribed and analyzed using a qualitative descriptive interpretive approach combining thematic content analysis and constant comparison methods 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 and adding 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. 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 calcium channel blockers prescription and per unit reduction in blood pressure for high-risk patients. However, additional modeling will be conducted to extrapolate these trial-based cost effectiveness findings into estimates of cost per life year saved and cost per Disability Adjusted Life Year averted. 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.

## **SELECTION AND ENROLMENT OF PARTICIPANTS**

### **POPULATION AND STUDY SITES**

Dangxiong County in Tibet autonomous region located in southwest China and rural Haryana (Faridabad district) state in North India respectively will be selected as study sites. These two sites fulfill the following criteria 1) **High CVD burdens**: for example, the hypertension prevalence among adults 40 and older in Yangbajing township in Dangxiong County was as high as 49.6%. Even in rural India, the leading cause of death (32%) is reported to be diseases of circulatory system; 2) **limited resources**: There are huge unmet needs for CVD prevention and management at the village level due to lack of trained CHWs and lack of chronic disease care delivery through the Primary Health Centers;

3) either **having CHWs** already in place or able to identify qualified candidates to be trained to fulfill the roles and responsibilities of CHWs; and 4) **having certain governmental awareness and support** to address CVD problems owing to previous programs in these areas such as the Tibetan studies and the risk factor prevalence study conducted by the Indian investigators in Haryana. These programs also help to ensure the success of this pilot demonstration project proposed here.

## **INCLUSION CRITERIA**

All participants above the age of 40 will be approached to participate regardless of gender, ethnic group, denomination, or other factors to assess their cardiovascular risk status. From this group subjects having elevated cardiovascular risk will be eligible for enrollment in study. High cardiovascular risk will be defined as:

- History of coronary heart disease, ischemic stroke, or hemorrhagic stroke, or
- Older age - 40 years or older (40+) and having diabetes mellitus, or
- Older age (40+) and systolic blood pressure  $\geq 160$  mmHg on two occasions at least one day apart.

## **EXCLUSION CRITERIA**

The research proposes to study adults at high risk for cardiovascular disease, and excludes adults below the age of 40 years. Additional exclusions are:

- Subjects with cardiovascular diseases complications who cannot be managed at primary care settings
- Subjects having Malignancy or life-threatening diseases;
- Bed-ridden subjects;
- Currently participating in a clinical trial; and
- Subjects having plans to move in the next 1 year

## **STUDY ENROLLMENT PROCEDURES**

The goal is to recruit participants from each of the 20 villages in India for a total sample size of 1,200 participants. Similar number of subjects will be recruited in the China as well. 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 hospitalization and event history in the past year.

Potential participants will be contacted in person at their residence to determine their interest in the study. They will be briefly told about the study, and if interested, they will be invited to take part the study through the informed consent process. If the consenting participant meets eligibility criteria, he/she will be enrolled in the trial.

## **INFORMED CONSENT**

During the baseline assessment carried out in the villages the research team will obtain written, informed consent from all participants who are eligible to participate in the trial. A single participant information sheet and consent form will be used for all the procedures done as part of the intervention and follow-up. We anticipate that most participants will be literate in Hindi and/or English.

The information sheet and consent form will be given to the potential participant and consent details will be explained, including: purpose of the trial, screening and study procedures, benefits and risks, confidentiality terms, and rights of the participant, and trial contact information. The research staff obtaining consent will ask questions to the participant about his/her understanding of what was explained to ensure that the participant correctly understands the PIS-consent information. The individual will be given the opportunity to review the document and any questions or concerns will be addressed. Participation is purely voluntary with no coercion and no material



compensation. All participants will be assured that they have the right to voluntarily withdraw from the study at any time, without any repercussions by way of this action affecting their future medical care.

If the individual agrees to participate in the trial, two copies of a signed consent form will be made, with the signatures of the participant and the site investigator (PHC Physician). For those who cannot read, the details of the study will be explained to the participant and informed consent will be obtained by the participant's thumb-print and proxy signature by a legally acceptable representative (LAR). In the absence of a LAR, a literate third party (non-study staff) may act as witness. One copy of the consent form will be given to the participant to keep and another copy will be kept in locked storage at PHFI. These consent procedures will be reviewed and approved by the institutional Ethics Committee (IEC) of PHFI for the India component of the study.

## **RANDOMIZATION**

In India, 20 villages will be selected to participate in the project. We do not plan to impose any geographical restrictions on the selection of villages for them to be not adjacent to each other because we expect the risk of contamination is small. The intervention, albeit highly simplified to suit local contexts, will be hard to imitate by those in 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.

In India, 9 villages will be randomized into the intervention group while 11 into the control group from Faridabad District, Haryana. For the entire study, there will be 09 intervention villages in India and 14 in China and 11, 13 control villages in India and China respectively. Randomization will be stratified by country.



2. **Simplified management scheme:** This scheme is based on an *absolute risk-based* approach, now the preferred means of delivering clinical interventions for cardiovascular prevention in developed countries. The shift to absolute risk-based approaches is also gaining momentum in developing countries and is an underlying theme of the recommendations in the more recently updated evidence-based national and international guidelines. The management will emphasize the importance of 1) identifying high-risk patients and referring patients when necessary; 2) providing 2 therapeutic lifestyle recommendations focusing on salt intake reduction and smoking cessation and referral for prescription of 2 medications (aspirin and calcium channel blockers ), when appropriate. The combination of these measures can be coined as *the “2+2” model*; and 3) following up these high-risk patients on a bi-monthly or more frequent basis. Though all individual measures are based on previous scientific evidence with no need for further research, the implementation and translation of the *2+2 model* into real-world settings remain to be investigated, which is the primary aim of this proposal.
3. **Systematic training of CHWs:** Enhancing the capacity of grass root healthcare workers through systematic training is a key feature of the interventional model. All training will be standardized yet adaptive to the local environment. A “train the trainer” model will be adopted with bilingual trainers recruited when necessary so that they can receive the central training in Hindi first and then deliver training to CHWs. The local training will consist of intensive initial training lasting 5 days followed by shorter refresher training at 6 months. Whenever appropriate, training will utilize participatory and interactive learning such as case studies, simulations, and role plays. After the initial intensive training, a test will be given and only those passing the test can receive the qualification necessary to implement the intervention. The PHC physicians, albeit having more experiences and higher capacity than CHWs, will also be included in and benefit from the training. The teamwork of physicians and CHWs is expected to provide better care for high-risk patients.

4. **Healthcare system strengthening:** Based on prior studies and our previous experiences, training *per se* will not provide all the necessary conditions for effective implementation of the training received. Several system-level approaches will be implemented. a) The intervention will integrate the services of Primary Health Center Physicians with village CHWs. CHWs will screen and refer (when necessary) patients to PHCs for medical treatment to the patients and technical support to the CHWs for them to follow up the patients. b) An Electronic Decision Support Software application will be provided to the Physicians and CHWs which will be compatible to both laptops and smart phones. The EDS will incorporate treatment guidelines and management algorithms which will help the physicians and CHWs in screening, risk stratification and provide automated decision-support prompts of guideline-recommended processes of care (e.g. treatment plan, laboratory tests, screenings) tailored to the participant's compliance. The EDS will store serial data in accessible software programs and will stimulate better continuity and more comprehensive care delivery. In addition, the EDS will have the following features: secure, password-protected access; electronic data capture from remote clinic sites; programming for quality assurance checks; utility to export to statistical software; validation tools for data-entry; and encrypted transfer facilities; and c) Lastly, performance feedback and economic incentives have been shown to enhance the effect of training and motivate recipients to better adherence of management schemes. Healthcare workers will be asked to record key patient management information on simple paper-based forms. These forms will be monitored by trainers and study team staff in order to provide healthcare workers with feedback on their performance. Performance-based payment will be made to them according to locally accepted scale.

## STATISTICAL CONSIDERATION

Key underlying assumptions for this study are: there will be 9 interventions villages and 11 control villages with an estimated total of 1200 high risk individuals from all the villages at baseline; an intra-

cluster correlation coefficient (ICC) of 0.01 or 0.02 and two-sided alpha=0.05. For the primary outcome, assuming the proportion of calcium channel blockers prescription 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).

## **SAFETY ASSESSMENTS**

The CVD risk reduction strategies of the intervention are not implementing any new drug or invasive procedure that requires specific monitoring of safety parameters. Rather, the intervention is a preventive health study that is enforcing existing, simplified evidence-based CVD risk management program. The control group will follow the existing standard care provided at the Primary Health Centers, while the intervention is designed to reinforce the care delivery through Community Health Workers and follow-up plan to achieve CVD risk control through salt reduction, quitting tobacco, and drug therapy.

## **ADVERSE EVENTS**

Definition of an Adverse Event: “An adverse event (AE) is any untoward medical occurrence in a subject temporally associated with participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.”

*List of Adverse Events:*

1. Side-effects of medications (calcium channel blockers , aspirin; and others per Investigator discretion)
2. Drug allergy /drug interactions

## **REPORTING PROCEDURES**

Information about the occurrence of any AEs will be sought at all scheduled visits. When an AE occurs, the Project Manager should ensure that the AE is reported within 7 working days to the PI by completing an Adverse Event Form and with notification by telephone. The PI will document the AEs with appropriate follow-up reports and final resolution forms with supporting documents. Anticipated AEs or those unrelated to the study intervention will be reported to the same individuals/entities on a monthly basis.

## **DATA COLLECTION AND QUALITY ASSURANCE**

Participant information collected for the trial is recorded on the appropriate Case Report Forms (CRFs) and entered into the database via the corresponding electronic Case Report Forms (eCRFs) found in the electronic health records (EHR) component of the EDS, which also serves as the web-based data management system.

## **DATA MANAGEMENT**

Under the supervision of the Project manager, a data management system will be administered by the data administrator and statistician. They will execute timely transfers, confirm receipt, organize, and back-up all study data. The data management system for the trial is in-built since the EDS is web-enhanced and encompasses the following features: secure, password-protected access; electronic data capture; automated edit tracking; programming for quality assurance checks; utility to export to statistical software; validation tools for data-entry (split screen views); and encrypted transfer facilities. In addition, the Project manager will monitor study enrollment, loss to follow up, adherence and satisfaction with intervention.

The database server for the Indian component of the study will be located at CoE-CARRS in New Delhi. The server will have restricted-access, and regular back-up schedules and appropriate server security procedures (to ward off unauthorized data retrieval attempts) will be instituted. All study participants will be identified by unique digit-based numeric. These regulations that ensure complete patient and data safety and confidentiality will be instituted and documented meticulously.

## **QUALITY ASSURANCE**

The study will be conducted in accordance with the International ICH Guidelines for Good Clinical Practice with all relevant local, national, and international regulations

## **TRAINING**

The New Delhi CoE will be responsible will be for data accuracy, consistency and quality pertaining to the India component while China CoE will be responsible the China component. All the research staff will be trained on the study protocol and procedure manuals before the start of participant recruitment. Study data derived from participant visits will be collected using standardized tools and instruments, with internal quality control protocols and subject to external quality verification through training.

All research staff will be trained on the study protocol and procedure manuals before the start of participant recruitment. In the event of incomplete, incongruous or ambiguous data, the Project Manager will be contacted for clarification by the Investigators who will monitor study data and participant safety.

## **TRIAL DOCUMENTATION / DATA QUALITY**

The Principal Investigator will maintain an on-site study binder (Trial Master File) that will contain the trial protocol, Procedure Manual, Patient informed consent form, Institutional Review Board document, medication records, general trial correspondence and participant screening logs, for

reference. All required study information will be recorded on source documents or the appropriate worksheet and corresponding eCRF. Case Report Forms and biological samples will be labeled with a unique study identifier. Ten percent of CRFs will be duplicated and the copy will be used for double data entry. All quantitative data will be entered into a My SQL database and audited for accuracy. Coded forms will be kept separately from the code list to maintain confidentiality. Study staff at the will check missing and outlier values monthly. All forms will be stored in a locked file cabinet in a secured office.

All worksheets, supporting source documents and administrative records will be retained by the PHFI for a minimum of three years (as per the amended Schedule Y Guidelines: Drug and Cosmetic Rules, 1945) following the last notification of approval by an appropriate regulatory authority.

## **MONITORING**

During the study, representatives of the Study Steering Committee will visit all the study sites on at least 3 occasions in the first year and on at least two occasions each year thereafter. The purpose of these visits will be to ensure that the study is conducted according to the protocol and good clinical practice guidelines are being followed. The sequality control reviews will also inspect study records and source documents for specific verification of participant details, data quality, and completeness of intervention implementation.

Access to Case Report Forms, source documents, and other study files will be made available for monitoring and audit purposes at these monitoring visits during the course of the study and after the study. Any deviations will be documented by the assigned monitoring personnel.

## **PARTICIPANT RIGHTS AND CONFIDENTIALITY**

*Institutional Review Board (IRB) Review*



This protocol and the participant information sheet-informed consent document and any subsequent modifications will be reviewed and approved by the respective ethics committees of the CoEs. In China, the Institutional Review Board of the George Institute for Global Health will oversee the ethical conduct of the study. In India the Institutional Ethics Committee of the Public Health Foundation of India (PHFI), will be responsible for oversight of the study. In addition, the study will be implemented with the concurrence of the India's Health Ministry's Screening Committee (HMSC).

#### *Informed Consent Form*

A signed consent form will be obtained from each participant. For participants who are illiterate, a (legally acceptable representative (LAR) or 3rd party witness must also sign the consent form. The consent form describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record.

The database server and additional off-site servers will both be housed in restricted-access buildings. Paper CRFs will be stored in locked cabinets in similarly secured buildings at participating clinics and will be accessed only by permitted study staff and the monitor from the RCC. Names and other easily recognizable identifiers will be removed from all CRFs prior to data entry and analysis. Instead, participant identification numbers (PID) will be used so that data and specimens may be linked; these are not meaningful to casual observers without access to the original study logs (accessible only to permitted research team). Any data, specimens, forms, reports, video recordings, and other records that leave the Clinic Site will be identified only by the PID to maintain confidentiality. All data files will be maintained under password protection at all times. All paper records will be kept in a locked file cabinet. The study records will be available to regulatory agencies, including IECs, ICMR, and OHRP. The funder, NHLBI, also have a right to access the study records.

## STUDY DISCONTINUATION

The study may be discontinued at any time by the IECs, ICMR, NHLBI, the OHRP or other applicable agencies as part of their duty to ensure that participants are protected. All study staff will be trained in procedures to minimize the potential for breaches of confidentiality, including but not limited to, ensuring that all files are closed and no conversations about individual study participants occur in public settings.

To ensure safety of the data, the respective project managers at China and India CoE will administer all transfers, organization, storage and back-up of study data. They will work closely with site coordinators and participating investigators to ensure all data are secured and any edits can be tracked using: password-protected access; automated edit tracking; audit trails; validation tools for data entry (split screen views); and encrypted transfer facilities. The project managers will monitor study enrollment, adherence and satisfaction, as well as adverse effects. Adverse events that occur during the present study will be brought to the attention of the PIs and appropriately addressed.

Participants will be referred to emergency care or any medical intervention, as deemed appropriate. In the event of significant risks or benefits to human subjects or decreased likelihood of study completion, the investigators may consider recommending discontinuation of research studies.

The database server and additional off-site servers will both be housed in restricted-access buildings, while paper copies of questionnaires will be stored in locked cabinets in similarly secured buildings. Names and other easily recognizable identifiers will be removed from the final datasets prior to data analysis. Numeric study identifiers will be used and these codes are not meaningful to casual observers without access to the original study logs. All data files will be maintained under password protection at all times. Study subjects can thus be assured that information revealed by them during an interview or collected as part of the examination will be kept confidential and cannot be subpoenaed or obtained by legal means except with their permission. All moderators and interviewers will be trained in procedures to minimize the potential for breaches of confidentiality.

## STUDY ORGANIZATION

The project will be managed on a day-to-day basis by an **Operations Committee** consisted of the PI and project manager in China and India. High level decisions about the direction and broader operation of the initiative will be made by the **Steering Committee** comprised of nominated co-investigators from China and India. Both committees will be chaired by Dr. YAN Lijing from the China CoE. The **Publications and Policy committee** to be co-chaired by the PIs of the COEs - Dr. WU Yangfeng and Dr. D. Prabhakaran - will take responsibility in matters relating to disseminations of study results, advocacy, and health policies.

## FUNDING

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