STUDY PROTOCOL

"Đương đầu với bệnh Tăng huyết áp ở Việt Nam: Giải pháp từ Y tế cơ sở

(Conquering Hypertension in Vietnam:
Solutions at Grassroots Level)

Short Name: Vietnam Hy-TREC (1U01HL138631-01)

Vietnam Health Strategy and Policy Institute

2017-2022

Abbreviations

LMIC: low, middle-income country

RCT: Clinical controlled trial

NCDs: Non-communicable diseases

CVD: Cardiovascular disease

HTN: Hypertension

DVD: Digital video disc

CHW: Community health worker

FULL PROTOCOL TITLE

Đương đầu với bệnh Tăng huyết áp ở Việt Nam: Giải pháp từ Y tế cơ sở (Conquering Hypertension in Vietnam: Solutions at Grassroots level)

Principal and Key Investigators:

Contact PI: Duc Ha, MD, MS, Dr.PH, is Vice Chief of Cabinet Office, Secretary of Minister of Vietnam Ministry of Health, and Senior Research Scientist at Health Strategy and Policy Institute (HSPI).

Multi-PI: Oanh Tran, MD, PhD is Director of HSPI, Vietnam Ministry of Health.

Multi-PI: **Jeroan Allison, MD, MSc Epi,** is founding Vice Chair of the Department, and Professor of Quantitative Health Sciences (QHS), at the University of Massachusetts Medical School (UMMS) and Associate Vice Provost for Health Disparities Research.

Study Investigator: Robert Goldberg, Ph.D. is Professor and Chief of the Division of Epidemiology of Chronic Diseases and Vulnerable Populations in QHS, UMMS.

Study Investigator: Tom Houston, MD, MPH, is Professor and Chief of the Division of Health Informatics and Implementation Science in QHS, UMMS and is a practicing general internist.

Study Investigator: Hoa Nguyen, MD, MS, PhD (Co-PI) is an Epidemiologist at Baylor Scott and White Health and Assistant Professor in the Division of Epidemiology of Chronic Diseases and Vulnerable Populations in QHS, UMMS.

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STUDY TEAM ROSTER

HSPI	Name	Role	Telephone number	Email
	Ha Anh Duc	PI (contact)	0936265696	ddha04@gmail.com
	Tran Mai Oanh	MPI		
	Phan Hong Van	Research Assistant	0904804286	phanhongvan.hspi@gmail.com
	Nguyen Thi Thu Cuc	Project Manager	0943901375	vtanihe@gmail.com
	Nguyen Hoang Giang	Data Manager	0912377770	thucuc_moh@yahoo.com
	Pham Van Hien	Research Assistant	0983544345	hienpv@hspi.org.vn
	Nguyen Thang	Research Assistant	0982170587	nguyengiang.1705@gmail.com
	Truong Thuc Linh	Accountant	0982004518	truongthuclinh@hspi.org.vn
UMMS	Jeroan Allison	MPI		Jeroan.Allison@umassmed.edu
	Robert Goldberg	Investigator		Robert.Goldberg@umassmed.edu
	Thomas Houston	Investigator		Thomas.Houston@umassmed.edu
	Sharina Person	Biostatistician		Sharina.Person@umassmed.edu
	German Chiriboga	Project Director		German.Chiriboga@umassmed.edu
BSWH	Hoa Nguyen	Investigator	214-265-3778	Hoa.nguyen@bswhealth.org

PARTICIPATING STUDY SITES

Agency		Person in charge	Telephone	Email
Hung Yen Department of Health		Nguyễn Văn Tâm	0971361688	tam.nv.dp@gmail.com
An Thi District health center		Cáp Văn Thụy	0869395666	duphonganthi@yahoo.com.vn
1	Đa Lộc Commune health center	Vũ Thị Thắm	0986894001	Tramytexadaloc@gmail.com
2	Hồng Quang Commune health center	Vũ Thị Lan	01668731897	tramytexahongquanganthi@gmail.com
3	Hoàng Hoa Thám Commune health center	Nguyễn Thanh Chương	0985838439	Tramhoatham@gmail.com
4	Nguyễn Trãi Commune health center	Nguyễn Hồng Luyện	01232899375	Chithe1982@gmail.com
Văn Giang District health center		Đàm Thị Vui	0986565242	damvui85@gmail.com
1	Thắng Lợi Commune health center	Nguyễn Thị Ngọc	0973700616	ytethangloi505@gmail.com
2	Mễ Sở Commune health station	Lê Kim Hùng	01693666866	tramytemeso@gmail.com
3	Cửu Cao Commune health station	Triệu Văn Tường	01635333755	trieutuong94@gmail.com
4	Vĩnh Khúc Commune health center	Lương Duyên Hải	0981412999	haihuyen.882008@gmail.com
Khoái Châu District health center		Đỗ Văn Chiến	0888568799	yteduphongkchy@gmail.com
1	Tân Dân Commune health center	Nguyễn Thị Miên	0974013128	ttytkc.tyt.tandan@gmail.com
2	Đại Tập Commune health center	Phạm Hữu Tuấn	0979825028	ttytkc.tyt.daitap@gmail.com
3	Liên Khê Commune health station	Phan Đình Thi	01662873872	ttytkc.tyt.lienkhe@gmail.com
4	Nhuế Dương Commune health center	Dương Thị Hương	0915525452	ttytkc.tyt.nhueduong@gmail.com
Kim Động District health center		Lê Xuân Lịch	0934371058 01277385886	ytdpkimdong@gmail.com
1	Nghĩa Dân Commune health center	Nguyễn Hữu Kế	0986709173	tytnghiadankdhy@gmail.com
2	Phạm Ngũ Lão Commune health center	Ngo Thi Xuan		tytphamngulaokdhy@gmail.com
3	Hùng An Commune health center	Phạm Văn Sâm	0915661337	tythungankdhy@gmail.com
4	Ngọc Thanh Commune health center	Tạ Thị Thư	0906090784	tytngocthanhkdhy@gmail.com

SUMMARY

Study Title

"Đương đầu với bệnh Tăng huyết áp ở Việt Nam: Giải pháp từ Y tế cơ sở (Conquering Hypertension in Vietnam: Solutions at Grassroots level)" (Vietnam Hy-TREC)

Objectives

We propose to evaluate the implementation and effectiveness of two multi-faceted community and clinic-based strategies for the control of hypertension among adults residing in the rural Red River Delta region of Vietnam with uncontrolled hypertension.

Study Design and Trial Outcomes

We propose to conduct a cluster randomized controlled trial to evaluate the implementation and effectiveness of two multi-faceted community and clinic-based strategies for the control of hypertension among adults with uncontrolled hypertension residing in the rural Red River Delta region of Vietnam.

The primary outcome of this randomized controlled trial (RCT) is the change in systolic blood pressure (BP) levels between the time of baseline study enrollment to 12 months after trial enrollment. Secondary trial outcomes include the change in diastolic BP, proportion of patients with hypertension who had their blood pressure controlled, medication adherence, patient self-efficacy, implementation outcomes and costs (see Section 11.5 Study outcomes). Differences in these primary and secondary trial outcomes will be compared between patients with hypertension who were randomly assigned to the intervention versus comparison condition.

Trial Interventions

Selected communes (the smallest residential administrative unit in Hung Yen) (n=16) will be randomly assigned to the intervention (n=8) and comparison groups (n=8) and will each

receive a multi-level intervention modeled after the Vietnam National Hypertension Program, jointly developed by the Ministry of Health and the Vietnam Heart Association. Patient assignment is based on the commune in which they reside.

In addition to the Vietnam National Hypertension Program, patients in the intervention group will also receive three carefully selected enhancements which will be integrated into routine clinical care: (1) expanded community health worker services; (2) home blood pressure self-monitoring; and (3) a "storytelling intervention," previously developed and pilot tested for feasibility and effectiveness in Vietnam by our research team. The storytelling intervention consists of interactive, literacy-appropriate, and culturally sensitive multimedia storytelling modules for motivating behavior change through the power of patients speaking in their own voice. Based on patient preferences that emerged during our formative work with our partnering rural communes, the storytelling intervention will be delivered by DVD, with serial installments at baseline and at 3, 6, and 9 months after trial enrollment. We will pursue a multi-faceted strategy to support implementation of the Vietnam National Hypertension Program and the proposed study enhancements.

Study Population

Sixteen eligible communes in 4 districts in Hung Yen province will be randomly assigned to the intervention group (n=8) or comparison group (n=8). Each of the selected communes satisfy the following criteria: (1) have a community health center with a medical doctor; (2) are not currently participating in other studies for hypertension control; and (3) have a minimum geographic separation of 12 kilometers (7 miles) from all other study communes to minimize possible contamination. There will be 16 other communes that will serve as "back up" communes if the numbers of patients recruited from 16 selected communes are lower than target sample sizes (see Appendix 1: List of participating and back up communes).

Patient population: Consenting adult (≥18 years old) participants with uncontrolled hypertension (n = 680) will be assigned to intervention versus comparison status based on the commune in which they reside.

1. STUDY AIMS

Our **Specific Aims** are as follows:

1. Conduct a pre-implementation local needs assessment and formative planning in 16 partnering communes in Hung Yen province, Vietnam leading to a context-specific protocol for implementing the Vietnam National Hypertension Program in both intervention and comparison communes and proposed enhancements (expanded community health worker services, home blood pressure self-monitoring, and storytelling) in the 8 intervention communes only.
2. Implement a cluster RCT (Type I Hybrid Implementation Design) of 16 communes and 680 patients with hypertension randomized to either an intervention group (Vietnam National Hypertension Program plus 3 trial enhancements) or comparison group (Vietnam National Hypertension Program alone).
3. Compare the effectiveness and implementation success of the two approaches using data from multiple sources at multiple points in time, including blood pressure measurements, patient surveys, and interviews with clinic personnel and clinicians.

3.1. Main Hypothesis: At 12 months post-randomization, participants in the intervention group will have a greater mean reduction in their levels of blood pressure than those in the comparison group.

3.2. Mediation Analysis: Differential changes in blood pressure for the two study groups will be partially explained by implementation factors at the patient level (e.g., intervention

engagement, medication adherence, and lifestyle changes) and structural changes at the clinic level.

2. BACKGROUND AND RATIONALE

Vietnam is undergoing an epidemiological transition with the morbidity and mortality from non-communicable diseases having risen rapidly over the last two decades[1]. This transition can be attributed to changes in population size, socio-demographic characteristics, and increases in life expectancy[1-4]. Cardiovascular disease (CVD) is now the leading cause of death in Vietnam, accounting for 30% of all deaths annually in 2010[5,6]. Major risk factors for CVD including hypertension, diabetes, unhealthy diet, and overweight/obesity are either on the rise or at alarming levels in Vietnam[7,8]. National data released by the Ministry of Health in October, 2016 showed that the prevalence of hypertension (HTN) was more than 40% for those 50-69 years old and the general population consumed high levels of sodium in their diet[8].

A 2011 population-based survey by our study team in Thai Nguyen province revealed that the overall prevalence of HTN was 23%. Moreover, only 34% of those with HTN were aware of their condition, only 43% of those who were aware that they had HTN received treatment, and, of these, only 39% had their HTN controlled[9]. A recent community-based survey in Vietnam showed that the vast majority (96%) of private health care providers were unable to identify the essential questions to be asked of a patient with HTN[10]. Another national survey found that 44% of rural residents gave incorrect answers about the principal risk factors for CVD[11].

3. NEEDS ASSESSMENT STUDY

During the first 6 months of funding, we will conduct a needs assessment survey at participating study sites. We recognize the multi-level ecological context of our intervention with layers of influence on health status, health behaviors, and behavioral changes beyond the

individual. These include: (1) community (individuals and families), (2) participating organizations, (3) socio-cultural environment, (4) physical built environment, and (5) the broader policy environment.

The needs assessment survey will be based on the triangulation of multiple data sources, including databases documenting the prevalence and control of HTN in the study communes, and semi-structured interviews with clinicians, clinic staff, community health workers (CHWs), and community members. The structured interviews will ascertain perceptions of clinicians and clinic leadership about the evidence for treating HTN (evidence), strengths and limitations of the current environment for implementing new tools for HTN control proposed as part of our intervention (context), and specific approaches needed to overcome barriers to blood pressure control (facilitation). We will utilize NVivo qualitative analysis software to objectively identify and catalog the perceptions expressed in the abovementioned interviews. The interviews will be analyzed utilizing a grounded theory approach to identify central themes and concepts as they appear in interviews. The identified concepts will serve as a baseline to build upon the packaged narratives to be presented visually in the DVDs.

As part of the needs assessment survey, we will perform 21 full semi-structured, individual interviews in a randomly selected subset of three communes from the intervention sites and three communes (Appendix 1) from the comparison sites. This will consist of semi-structured interviews with clinicians, nurses, and leadership at the health centers and interviews with patients with uncontrolled HTN. We will work closely with the Department of Health in Hung Yen to identify stakeholders, who understand and are involved in hypertension management in the community and physicians who have managed HTN patients at the provincial and district hospitals to participate in the study. Patients with uncontrolled HTN will be referred by their physicians at the local hospitals.

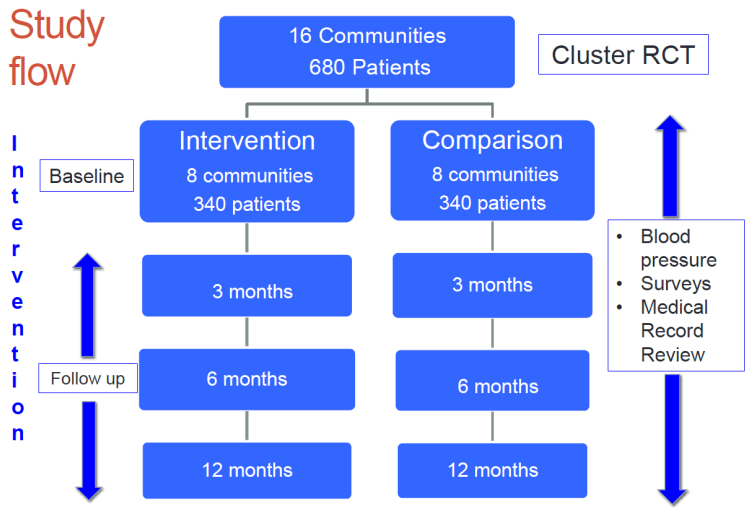
Brief structured qualitative assessments will be conducted at all remaining sites via the focus group discussions (FGDs). We will conduct 9 FGDs at 3 study communes. Details and tools for the individual interviews and FGDs can be found in the Manual of Operations.

These interviews will be repeated on three occasions to assess implementation progress, in study years 1, 3, and 5. We anticipate that after intervention implementation, the gaps in hypertension management found the needs assessment study conducted at the baseline interview will be narrowed, with a greater degree in the intervention group. Information on intervention acceptability, appropriateness, feasibility, and fidelity will be collected as well.

4. TRIAL DESIGN

- **Type/design of trial**: Cluster RCT with 2 arms: intervention arm (n=8 communes, 340 patients with uncontrolled HTN) and comparison arm (n=8 communes, 340 patients with uncontrolled HTN).
- **Study Outcomes:** The primary outcome of this RCT is the change in study participants' systolic BP levels from baseline trial enrollment to 12 months. Secondary outcomes include changes in diastolic BP, blood pressure trajectories, the proportion of patients with their HTN controlled, medication adherence, self-efficacy, cost, and implementation outcomes (see Section 11.5 Study outcomes)

Figure 1. Study Flow



- **Study population, groups/arms, and sample size**: This trial includes 2 arms: an intervention arm (n=8 communes, 340 patients with uncontrolled HTN- systolic BP>=140 mmHg or/and diastolic BP>=90 mmHg) and a comparison arm (n=8 communes, 340 patients with uncontrolled HTN).
- **Study location**: The study will be conducted at 16 communes in 4 districts in Hung Yen province in northern Vietnam (Appendix 1).
- **Duration of enrollment period and follow-up**: Intervention and comparison groups will undergo parallel assessments including standardized BP measurement and in-person surveys at baseline and at 3, 6, and 12 months post-enrollment. The enrolment will start in year 3 and finish in year 4. The total duration for enrollment and follow up for the study will be approximately one and a half years.
- **Intervention description**: Both study groups will benefit from implementation of the Vietnam National HTN Program and will receive implementation assistance as described in Section 6. The intervention group will receive three enhancements: Expanded CHW services, BP self-

monitoring, and the storytelling intervention delivered by DVD at the time of trial enrollment, and at 3, 6, and 9 months after enrollment. Specifically, CHWs will be trained in motivational interviewing and structured problem solving. Motivational interviewing, a behavior-change counselling approach, facilitates improvements in diet, exercise, adherence to medication regimens, tobacco use, and engagement. CHWs will also be taught simple techniques to help patients set goals for lifestyle changes, such as salt and alcohol reduction, smoking cessation, and increased physical activity and medication adherence and develop problem-solving strategies to achieve these goals. These intervention elements map directly to the adapted Chronic Care Model and PARiHS Model. During the study, the intervention group will receive home BP monitors and DVD players, which will be provided to comparison patients after the study has been completed, along with all other intervention materials.

After completion of the pre-implementation planning phase, we will have detailed protocols and written manuals for each component of the intervention and data gathering process that will be developed with substantial input from the local and international academic team, as well as from community-based health care providers and patients. Intervention and comparison patients will undergo parallel assessments including standardized BP measurement and in-person surveys at baseline and again at 3, 6, and 12 months post-enrollment. In this Type I Hybrid Effectiveness Implementation Design we will also collect information on the implementation portion of the study in anticipation of future dissemination of the trial intervention. Both intervention and comparison conditions will receive internal and external facilitation as part of the National Vietnam HTN Program.

- **Trial Randomization**: A total of 16 selected communes (detailed socio-demographic information of these communes are provided in Appendix 1) will be randomly assigned to either the intervention arm (8 communes) or comparison arm (8 communes). Study

participants with uncontrolled HTN (n = 680) will be assigned to intervention versus comparison status based on the community in which they reside.

5. SELECTION AND ENROLLMENT OF TRIAL PARTICIPANTS

Recruitment of trial participants will be based on the successful protocol from our pilot work. Sampling frames of all adult community members are available from the Hung Yen Department of Health. **:** Community residents will be invited to the commune health center for screening events via a public announcement to join a health project. Screening events approximately twice per month. Patients with elevated BP, defined as a systolic BP≥140 mmHg or diastolic BP≥90 mmHg at the time of the screening, will be invited for re-measurement over the next two weeks (minimum of 1 week apart between the 2 measurements). If they still have elevated BP at the time of the second clinic visit, they will be eligible for trial enrollment.

5.1 Inclusion Criteria

(1) residence in a study selected commune;

(2) at least 25 years old;

(3) presence of uncontrolled HTN based on the screening process described previously and

(4) willingness and ability to provide informed consent.

(5) residing in the commune in the next 12 months from enrollment.

5.2 Exclusion Criteria

(1) participation in another interventional study;

(2) pregnant (a negative test for women of child bearing age- – ascertained by test at follow up appointment);

(3) advanced cognitive impairment; or

(4) previous participation in developing or having exposure to the HTN storytelling modules;

5.3 Withdrawal of Study Participants

Participation in this study is voluntarily and patients can withdraw at any time during the study. Patients will be withdrawn from the study if they become pregnant. This information will be collected via patient's self-reporting, reviewing medical records and pregnancy testing at follow up visits.

5.4 Study Enrollment Procedures

A screening form including all inclusion and exclusion criteria will be used to screen patients. Data will be entered in the Redcap database. At the time of clinic screening, patient's BP levels will be measured by trained study staff in a standardized manner (Section 8) and study staff will explain the study protocol to possible participants and verbal consent will be obtained. A second screening visit will be scheduled for eligible patients with elevated BP (systolic BP≥140 mmHg, or diastolic BP≥90 mmHg) two weeks later (minimum of 1 week apart), at which time their BP will be re-measured and written informed consent will be obtained.

Individuals who are found to have elevated BP at the time of clinic screening and are not willing to participate in the study will be referred for usual care at local community health centers.

6. STUDY INTERVENTIONS

6.1 Intervention Components

Table 1. Intervention components by study groups

	Intervention Enhancements	**Intervention group**	**Comparison group**
1	**Vietnam National HTN Program** • Training for physicians and nurses • Patient education materials • Multi-media community announcements	Yes	Yes
2	**Expanded Community Health Worker Services** • Support and strengthen their role in motivating patients through lifestyle changes and antihypertensive medication adherence	Yes	No

3	**Home Self-Blood Pressure Monitoring** • Free home BP monitors • Record BP in a pre-tested log and share with their physicians and CHWs	Yes	No will be given BP monitor and BP log after the study has ended
4	**Storytelling Intervention** • 4 DVDs with stories from Stars: Baseline and 3, 6, and 9 months • Learn More Module	Yes	No (only 2 DVDs with Learn More Module) will be given 4 storytelling DVDs after the study has ended

6.1.1 Vietnam National HTN Program (Intervention and Comparison Groups).

The Vietnam National HTN Program is part of the comprehensive Vietnam National Strategy on Prevention and Control of Cancer, Cardiovascular Disease, Diabetes, Chronic Obstructive Pulmonary Disease, Asthma, and Other Non-Communicable Diseases, Period 2015-2025[12]. This multi-arm national strategy was approved by the Prime Minister in 2015 (Decision No 376), merging several national programs into a cohesive, integrated approach. The Vietnam National HTN Program was authorized by Decision # 172 in 2008.

The Vietnam National HTN Program includes various training sessions about HTN prevention and management for physicians and nurses (Appendix 2), and a comprehensive set of patient education materials, including brochures that are written in a culturally and literacy-appropriate manner, with ample graphic images. Multi-media community service announcements have also been prepared for local television and radio stations and newspapers, and will be implemented in both study groups**.**

6.1.2 Expanded Community Health Worker Services (Intervention Group Only).

CHWs are currently embedded in the clinical system for each of our partnering community health centers and across the nation. A critical enhancement for the intervention group will be to support and strengthen their role in activating patients to more actively manage their HTN through lifestyle changes and adherence to prescribed antihypertensive medication.

Specifically, CHWs will be trained in motivational interviewing and structured problem solving. Motivational interviewing, a behavior-change counseling approach, facilitates improvements in diet, exercise, adherence to medication regimens, tobacco use, and overall engagement in one's care[13]. When combined with other approaches, it amplifies the efficacy of other methods[14]. Motivational interviewing, which is frequently misunderstood as a therapeutic technique[15], focuses on developing a patient's intrinsic motivation to achieve goals that they set. Since motivational interviewing discourages advice-giving by the practitioner, CHWs without advanced healthcare training can be safely trained in this dynamic approach to facilitate health behavior change. Peers have been shown to meet or exceed health care professionals in motivational interviewing effectiveness[16,17].

CHWs will also be taught simple techniques to help patients set goals for lifestyle changes, including salt and alcohol reduction, smoking cessation, and increased physical activity, and optimal medication adherence; they will also develop problem-solving strategies to achieve these goals. General principles of goal setting involve the cyclic process of recognizing the need for change, formally establishing a goal, and engaging in goal-directed activity supported by self-monitoring and self-rewards[18]. CHWs will be taught how to work with patients to: (1) engender engagement and commitment by self-identifying goals that are meaningful and consistent with their personal lives and family context; (2) promote feasibility by identifying a limited set of goals and small, attainable steps; (3) provide educational resources; (4) establish a structure for non-threatening accountability and support through regular review; and (5) link goal attainment to changes in self BP monitoring for reinforcement. These techniques were successfully used in our pilot work[19].

As in our pilot work, CHWs will be taught how to use the storytelling intervention (below) to start conversations with their clients (Appendix 2). After each DVD of the storytelling intervention, CHWs will meet with the patient to review the material, elicit possible barriers to

lifestyle changes and medication treatment, and identify strategies to overcome recognized barriers. CHWs will make patient home visits to resolve difficulties related to viewing the DVDs, and they will keep detailed logs of their patient interactions to help provide a qualitative sense of intervention effectiveness and suggest approaches for improvement.

6.1.3 Home Self-Blood Pressure Monitoring (Intervention Group Only).

Home BP self-monitoring is the second enhancement for the intervention group. Patients assigned to this condition will receive free home BP monitors and will be instructed in their use by the CHW (comparison patients will receive home BP monitors and BP log after the study has ended). Patients will record their BP findings in a log previously developed and implemented by the study team (Appendix 3). Patients will bring the logs into participating clinics for review with the physician and CHW, consistent with the current approach to medical record keeping in our partnering rural community health centers which rely on written medical records. Our pilot work found that most patients did not have difficulty in adhering to these recommendations. Patients are routinely given a portable copy of their medical record with instructions to bring it to future clinic appointments.

Technology for BP self-monitoring is advancing rapidly. We will choose from several currently available BP monitors validated for accuracy and reliability based on protocols from professional societies[20,21]. Up-to-date lists of devices by validation status, with supporting references, characteristics, and price are available on the Internet[22]. Passing a validation test does not mean that a device will be accurate and acceptable for all patients[20]. Thus, study patients will receive their own device in clinic (with an appropriate arm-circumference cuff), at which time device accuracy will be checked against a sphygmomanometer measurement performed by research staff. CHWs will advise patients to measure their BP at home following a standardized protocol (Section 8.1). Readings will initially be taken in the morning after arising and again at night before going to sleep. Patients will be advised about reading variability,

cautioned about over reacting to a single elevated BP value, and given specific protocols for when to contact a health care provider should the need arise (Appendix 4. Protection of Human Subjects).

6.1.4 Storytelling Intervention (Intervention Group Only).

A novel storytelling intervention is the third enhancement for the intervention group, and this approach will be seamlessly supported by CHWs as described above. Our team has previously designed, implemented, and pilot tested such an intervention for improving HTN control in Vietnam[19,23]. The patient narratives included in the intervention materials include first-hand accounts from patients in their journey to gain control of their hypertension. The stories aim at connecting with viewers and begin a process of transportation, in which the patient can identify with the storyteller and any section of his/her narrative process in connection with the experience with hypertension. Additionally, the stories presented are complemented by additional formal information about hypertension control. This additional section is known as Learn-More in the intervention materials, which will be built on the stakeholders' opinions gathered via interviews and national experts in HTN. Preliminary evidence showed that the intervention was seamlessly integrated into the clinic work flow, met with great acceptability by staff and patients, and offered important potential for reducing patient's elevated BP levels. For our newly proposed work, we will supplement this previously developed material with new patient stories to represent our expanded community base. We will develop four DVDs, the first to be delivered to intervention patients at enrollment, with viewing in the clinic, followed by installments at 3, 6, and 9 months to be viewed at home. All intervention participants will be given a DVD player in clinic and instructed in its use and how to navigate the menu structure of the DVDs (patients in the comparison group will be given a DVD player and the DVDs after the study has ended). After each installment, we will administer a post-media interview to ascertain the frequency and duration of viewing, change in behavioral intentions, and overall satisfaction

with the intervention; these data will be used for the mediation analysis to describe implementation and mechanisms of intervention effectiveness (Section 8.6).

6.2 Intervention Delivery

6.2.1 Vietnam National HTN Program (Intervention and Comparison Groups)

There will be a series of training sessions, which will be carried out at local district or provincial health departments; research staff including physicians and nurses will participate in these trainings. Training sessions will be delivered in the collaboration with the Vietnam Ministry of Health.

6.2.2 Expanded Community Health Worker Services (Intervention Group Only)

There will be a series of training sections for CHWs, which will be carried out at local district or provincial health departments. Training sessions will be delivered in the collaboration with the Vietnam Ministry of Health.

6.2.3 Home Self-Blood Pressure Monitoring (Intervention Group Only)

The intervention group will receive home BP measurement devices at the time of trial enrollment at their community health centers. After obtaining informed consent, a trained CHW will instruct patients on how to use the BP measurement devices to measure their BP at home and how to record their BP readings in the BP Log. Trained CHWs will explain to patients how to read/understand the BP Log and when they need to contact their doctors and study staff for possible urgent care should they find their BP to be consistently elevated.

6.2.4 Storytelling Intervention (Intervention Group Only)

The intervention group will receive the storytelling intervention delivered by DVD at the time of trial enrollment and at 3, 6, and 9 months after enrollment During the study, the intervention group will receive DVD players, which will be provided to comparison patients after the study has been completed, along with all other intervention materials.

After obtaining informed consent, a trained CHW will introduce and explain the DVD to the patient and instruct them on how to use it at home. Initially, patients will view the first DVD installment at their community health center and then will engage in a post-media interview and problem-solving session with a CHW. After the first viewing at the clinic, patients will bring the DVDs home for further view.

At three and six months after trial enrollment, a second and third installment of the DVDs will be delivered at their community health center for home viewing by patients assigned to the storytelling intervention group. At nine months after trial enrollment, the fourth DVD will be delivered at participant's home by CHWs. After viewing the DVDs, a follow up visit will be scheduled for a "post-media" interview and re-measurement of their BP by a trained CHW.

Patients in the comparison group will receive the first DVD at trial enrollment and the second DVD at month 6 at their community health center.

6.3 Adherence Assessment

6.3.1 Vietnam National HTN Program (Intervention and Comparison Groups)

During the study period, study staff will record the numbers of training sessions, number of trainees at each training session, and timing of the various training sessions to ensure that the training is conducted per the Manual of Operations.

6.3.2 Expanded Community Health Worker Services (Intervention Group Only)

During each study period, study staff will record the number of training sessions, number of trainees at each training session, and the timing of the trainings to ensure that the training is conducted per the Manual of Operations.

6.3.3 Home Self-Blood Pressure Monitoring (Intervention Group Only)

The number of BP measurement devices and BP logs distributed to all study patients will be recorded. During each study period, local study staff and CHWs will call patients every two weeks to find out if they need any technical support for the BP measurement devices. They will

also encourage them to measure their BP on a daily basis and record their BP levels in the BP log daily to promote their adherence to the intervention. CHWs will check the BP log each time they visit patients at home or at the regularly scheduled follow-up visits at the community health centers.

6.3.4 Storytelling Intervention (Intervention Group Only)

The number of DVD players and DVDs distributed to all study patients will be recorded. During each study period, local study staff and CHWs will call patients every two weeks to find out if they need any technical support for the DVD players and will be encouraged to view the DVDs more frequently to link patients' stories to themselves, draw lessons and promote their adherence to the intervention. At the regularly scheduled follow-up visits at the community health centers, CHWs will conduct "post-viewing" patient interviews, which will ask about the frequency and time that patients viewed each DVD weekly at home, and their rating for each DVD.

7. STUDY PROCEDURES

7.1 Schedule of Evaluations

Assessment	Screening	Baseline, Enrollment, Randomization: Visit 1	Follow up 3 months Visit 2	Follow up 6 months Visit 3	Follow up: 12 months Final Visit
Verbal Informed Consent	X				
Demographics	X	X			
Blood Pressure measures	X	X	X	X	X
Written Informed Consent Form		X			

Assessment	Screening	Baseline, Enrollment, Randomization: Visit 1	Follow up 3 months Visit 2	Follow up 6 months Visit 3	Follow up: 12 months Final Visit
Medical History		X	X	X	X
General Physical Examination		X	X	X	X
Inclusion/Exclusion Criteria		X			
Enrollment/Randomization		X			
Vital Signs, Anthropometric Measurement		X	X	X	X
Participant Surveys		X	X	X	X
Medical records review		X	X	X	X
Implementation measures (eg. feasibility, fidelity appropriateness, adoption)	X	X	X	X	X
Costs	X	X	X	X	X

7.2 Description of Evaluations

7.2.1 Screening Evaluation

Since the patient enrollment process in the present study will be carried out on a rolling basis, it will start in the middle of Year 3 and continue until reaching the target sample size of 680 patients with uncontrolled HTN.

Screening will be carried out among eligible adult men and women >= 25 years old at each of the 16 participating communes. Based on available census lists, community residents will be randomly selected for the screening of their BP by study staff. Verbal consent will be obtained at this time. The number of participants screened, number of participants with elevated BP (systolic BP≥140 mmHg or systolic BP≥90 mmHg), and the number of participants invited to the next visit at the local community health center for re-measurement of their BP levels will be recorded (minimum 1 week apart).

7.2.2 Study Enrollment and Baseline Data Collection Activities

Enrollment

Patients with elevated BP at the initial clinic screening exam will be invited to their local clinic to learn more about the study and have their BP re-measured over the next two weeks. Patients with elevated BP at the time of the second BP measurement, and who satisfy the other trial inclusion criteria, will be eligible for trial enrollment and invited to participate in the study. Written informed consent will be obtained from all patients by trained study staff. The number of eligible patients with uncontrolled HTN and number of enrolled patients will be recorded.

Baseline Assessments and Follow up

At the baseline clinic exam and at the 12 months follow up visit, trained study staff will collect the following information (detailed methods for data collection can be found in Section 11 and in the Manual of Operations) :

- BP findings
- Anthropometric Measures: height, weight, waist and hip sizes
- Surveys that have been translated into Vietnamese and validated in the feasibility trial:
    - WHO STEPs will be used to collect data on risk factors for CVD including tobacco use, alcohol consumption, salt intake, and physical activity[24,25]. In our study, the STEPS questionnaire includes two different steps of risk factor assessment: Step 1 (questionnaire), Step 2 (physical measurements). The research team members will first gather the information on socio-demographical background, behavioral risk factors, NCD-related medical history of the participants. To support interviewers to measure and convert some behavioral indicators into standard units, a set of pictures will be used including: Showcard for vegetable, fruits intake; Showcard for alcohol consumption. After that, the physical measurement will be conducted by physicians who are working at selected local commune health stations. These physicians will have been trained by the research team members following GCP principles through the site initiation training. The tools for physical measurement include: (i) Digital automatic blood pressure monitor; (ii) Standard electronic scales; and (iii) Standard Stadiometer and Constant Tension Tape Measure for measuring height and waist circumference. These tools are recommended by clinical experts of the National Hypertension Control Program and validated by provincial Department of Health

      Adherence to anti-HTN medications will be collected using a survey designed by Duke University. This new, validated measure, looks at extent and reasons of non-adherence separately, which in longitudinal assessments may offer a more refined panorama of behaviors related to medication-taking[26].

- Self-efficacy in HTN management will be measured by the Medication Adherence Self-efficacy Scale (MASES) instrument[27,28].

- Quality of life will be measured by the short form 12 questionnaire Health survey (SF-12)[29].

- Post-DVD viewing interviews for intervention participants will be based on protocols previously developed by our team[19].

- Medical record review will ascertain values for patient's serum lipid profile, serum glucose, medical co-morbidities, currently prescribed medications, and pregnancy status.

- Implementation data gathered by the research coordinator and CHWs that will inform progress toward specific study milestones

- Semi-structured interviews for qualitative data (e.g., semi-structured interview, focus group discussion) to collect data on patient's engagement with the study intervention enhancements, barriers for adherence to the intervention enhancements, and suggestions.

- Piggybacked items for cost data at all qualitative participant surveys including cost for drugs, diagnostic procedures, time lost, health center visits, and consultation fees.

Randomization

- A total of 16 communes will be randomly assigned to either the intervention group (n=8) or comparison group (n=8). Study participants will be assigned to intervention versus comparison status based on the community in which they reside (not individual patient randomization).

7.2.3 Follow-up Visits

- Patients will be followed up at 3, 6, and 12 months after trial enrollment. Information collected at the time of baseline trial assessment will be collected at each clinic follow-up visit (STEPs, Self-efficacy in HTN, Quality of life, and cost will be at collected at 12 months only).

7.2.4 Completion/Final Evaluation

- The 12 month visit is the final visit. Data collected at the final visit is described in Section 7.2.2

8. DATA COLLECTION AND QUALITY ASSURANCE

8.1 Data Collection

Data sources include: (1) standardized BP and anthropometric measurements at baseline and at 3, 6, and 12 months after trial enrollment; (2) quantitative participant surveys at baseline, 3, 6, and 12 months after enrollment; (3) post-media interviews after each installment of the storytelling intervention for the intervention group; (5) medical record review; (6) implementation data gathered by the research coordinator and CHWs that will inform progress toward specific study milestones (Section 13); (7) semi-structured interviews for qualitative data; and (8) piggybacked items for cost data at all qualitative participant surveys.

Blood Pressure and Anthropometric Measurement. As previously described in Section 7, all certified study nurses will be trained to measure BP according to a standardized protocol approved by the World Health Organization (Appendix 4) and currently implemented by the NIH Coronary Artery Disease In Young Adults (CARDIA) study. The detailed protocol is available at www.cardia.dopm.uab.edu. We used this protocol in our previous randomized trial of storytelling (CSI: Birmingham)[30] and in our pilot work in Vietnam. This protocol was written for use with the

OmROn HEM907XL automated BP monitor, with special attention to assessment and maintenance of the instrument's accuracy and training/certification of research assistants. Using a proper cuff size, measurements are taken after sitting quietly for 5 minutes, with the arm supported on a flat surface, with the upper arm at heart level. The patient's back should be supported, and both feet should be flat on the floor. Three measurements are separated by at least one minute, and values from the last two measurements will be averaged.

Height and weight will be measured in the absence of shoes and heavy clothing while waist and hip sizes will be measured by placing the tape horizontally around the smallest part of the waist and the widest portion of the hips, respectively.

Participant surveys. All survey items will be taken from validated instruments, with scales or sub-scales left intact to preserve psychometric properties[31]. Many of the survey measures previously existed in Vietnamese or have been translated and tested by our team as part of our previous work[19]. The survey will be implemented in a computer-assisted format and pilot tested for acceptability. The target duration time for the final survey will be less than one hour. We will collect information on patient's level of education, occupation, and economic circumstances using the WHO STEPs protocol,[24] which has been used to investigate the epidemiology of HTN in the Vietnamese language.[32] STEPs will also be used to collect data on CVD risk factors including tobacco use, alcohol consumption, salt intake, and physical activity. Adherence to anti-HTN medications will be measured by forms previously developed by Duke University[26]. The Medication Adherence Self-efficacy Scale (MASES) instrument[27,28], also translated by our team, will measure self-efficacy in HTN management. Quality of life will be measured by be measured by the short form 12 questionnaire health survey (SF-12)[29].

Post-DVD viewing interviews for intervention participants will be based on protocols previously developed by our team (Appendix 4). The post-DVD viewing interviews using a structured questionnaire will collect self-reported engagement with the DVDs, including total

viewing minutes, specific segments that were viewed, and whether the DVD was shared with family or friends. “Transportation” is a validated concept measuring absorption into the video story that has been linked to intervention effectiveness and is measured by a validated scale[33,34]. Participants will be asked to elaborate on what motivated/hindered their intervention engagement.

Translation of Survey Instruments. We recognize the complexity involved in translating survey instruments and data collection protocols. Therefore, we will follow the set of best practices developed by the U.S. Census Bureau.[35] Translation will be accomplished by a translation team, with multiple versions prepared in parallel followed by team meetings to reconcile possible differences. This approach has been shown to be superior to the simple “back-translation approach” in which translation by a single individual is translated back into the source language for review of accuracy[36]. As in our previous work, Drs. Nguyen and Ha will lead the translation team, each being bilingual in both Vietnamese and English.

Translation will include cognitive interviews with five participants drawn from the local community. Cognitive testing will identify constructs specific to the Vietnamese language and culture so that appropriate adjustments may be made to ensure cross-cultural equivalence.[37] Several cycles of revision will be accomplished at full translation committee meetings conducted in person and by Internet video link. The ultimate aims of the translation process will be to produce a product that: (1) is reliable with semantic equivalence, technical accuracy, and textual completeness; (2) reads with fluency with a natural flow in Vietnamese; (3) is appropriate to the literacy level of the intended audience; and (4) is appropriate in style and tone.

Survey Protocol. Based on our pilot work in Vietnam, survey data will be collected by research assistants and CHWs who will record data into an encrypted computer at the point of interview.[38] Following training, interviewers will conduct practice interviews until certified by the trial supervisors. Use of a tablet or laptop computer provided by the study will promote data

quality by: (1) prompting the interviewer to adhere to a standardized script; (2) presenting branching questions tailored to the participant's real-time responses; and (3) checking for data entry errors, such as out of range responses. Standardized protocols, rigorous training, and built-in redundancy checks will ensure the quality of the survey data. REDCap, an Internet-enabled database which is available at no cost, will be used for all data collection activities. The data collection will be paper-based; then, all paper questionnaires will be entered into and managed through the REDCap web-based data management system. After the initial surveys have been programmed into REDCap, the data collection protocol will be iteratively refined by pilot testing. We will implement "reproducible research" principles, with extensive documentation and standard operating procedures enabling outside investigators to replicate all findings (http://www.cdisc.org). Data will be stored on a Health Insurance Portability and Accountability Act (HIPAA) -compliant secure server with daily backup at HSPI.

8.2 Data Management

Data will be stored on a secure sever at HSPI and managed by the study data manager who is familiar with the REDCap database. This person will work closely with the PIs and experts at UMMS to make sure that the data are managed properly.

Missing data: Missing data may introduce potential bias, and the most important defense to minimize missing data on key factors is advanced planning[39,40]. In our previous work, we have developed successful plans to maximize participant retention and obtain complete data through sound principles of data collection and quality control[19]. Sensitivity analyses will estimate the bounds of potential bias introduced by omissions. Under the missing-at-random assumption, multiple imputation[41] will generate plausible values of missing covariates while accounting for the additional uncertainty introduced by the omissions.

8.3 Quality Assurance

8.3.1 Training

At the beginning of the study, all study staff will be extensively trained in the overall study protocol and related procedures by the PIs and key investigators. The study staff will be trained about the needs assessment study protocol, overall trial protocol prior to conducting the formal trial including Manual of Operation and Good Clinical Practice,

8.3.2 Quality Control Activities

Trained research assistants and CHWs will record all survey data into an encrypted computer/tablet at the point of interview[38] via the Internet into a pre-programmed and pilot-tested REDCap database[42]. Following training, interviewers will conduct practice interviews until certified by their supervisors. We will implement "reproducible research" principles, with extensive documentation and standard operating procedures enabling outside investigators to replicate all of our trial findings (http://www.cdisc.org). Data will be stored on a HIPAA-compliant secure server with daily backup at the HSPI. Each patient will be assigned a study ID at the beginning of the study.

8.3.3 Protocol Deviations

Study deviations will be documented in careful detail by the project manager and reported to the HSPI's IRB and the Steering Committee and DSMB, and will be discussed during regular committee meetings. The Steering Committee (Section 14) will recommend appropriate actions to ensure that protocol deviations will be minimized.

8.3.4 Monitoring of Trial Progress

Members of the HSPI team will conduct a monitoring visit to study sites every six months, and the NHLBI project scientist will conduct a monitoring visit to Vietnam every year. In

addition, outside monitoring across Hy-TREC sites will be conducted. The monitoring visits will evaluate study site performance based on predefined implementation outcomes including participant enrollment, intervention implementation, data collection, follow-up rates, documentation of AEs and SAEs, and accompanying reports. After a monitoring visit, a report will be prepared and shared with the Steering Committee and DSMB for purposes of making any needed adjustments for enhanced trial implementation.

9. SAFETY ASSESSMENTS

Details of any possible adverse events associated with trial participation can be found in the Human Subjects Research document (Appendix 5). In brief, we anticipate minimal risk of inappropriate disclosure of protected health information and/or personal identifiers to anyone other than properly trained investigators with a demonstrated “need to know.”

During the focus groups, the primary risk will be possible discomfort in sharing personal information in a group setting. This will be mitigated through the use of skilled moderation and all participants will be allowed to terminate participation in a focus group at any time. We anticipate very minimal risk for participants in the intervention group.

During the conduct of the various questionnaire surveys, patients may become uncomfortable when asked about psychosocial factors such as depression or anxiety. Patients will be reminded repeatedly that they are under no obligation to respond to any question, and interviewers will be trained, certified, and supervised in appropriate interview techniques. In addition, interviewers will be trained to recognize responses suggestive of imminent risk (e.g., patient suicidal ideation) and how to immediately contact medical personnel for help.

Risk from participation in the randomized trial may be related to potential psychological distress related to home BP self-monitoring. However, patients will be instructed in the use of proper protocols for obtaining accurate measurements of their BP. They will be provided with explanations about normal biologic variability of BP readings and given explicit instructions about when to seek medical advice because of abnormal BP findings, or because of symptoms of concern such as chest pain or shortness of breath. Trained clinical personnel will be available to answer questions 24 hours a day. In addition, participants may experience discomfort from setting behavioral goals that are too challenging. However, all exercise and dietary protocols will be individually approved by clinicians at the health center, and the CHWs will be taught how to work with patients to set modest, incremental goals and to stop at the first signs of discomfort. Patients will also be taught the warning signs of acute cardiovascular syndromes, such as chest pain or shortness of breath, and how to seek urgent medical care when necessary. Safety will also be promoted by frequent follow-up between trial participants and the local CHWs.

9.1 Specification of Safety Parameters

Safety parameters include patients' BP levels and severe clinical signs and symptoms. Patient's level of BP will be considered too high if their SBP exceeds 180 mmHg or DBP exceeds 120 mmHg according to clinical guidelines issued by the Vietnam Ministry of Health. Patient's BP level will be considered too low if their SBP < 90 mmHg or diastolic BP < 60 mmHg. Severe clinical signs and symptoms include any symptoms suggestive of acute cardiac disease including chest pain, shortness of breath, orthopnea, syncope, or rapid increase in edema or any symptoms suggestive of acute neurologic disease such as new onset of numbness, tingling, or weakness in the limbs or face, dysarthria, visual disturbance, or vertigo.

9.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

At the beginning of the study, patients are advised to measure their BP levels on a regular daily basis. Patients should seek medical care immediately if their BP levels are either too high or too low as defined in Section 7.1 and should report these findings to CHWs and study personnel. The study personnel will record these events in the study database and provide a regular report to the PIs. The safety parameters will be analyzed during regular DSMB meetings or right after safety data are available if urgently needed.

9.3 Adverse Events (AE) and Serious Adverse Events (SAE)

All patients enrolled in the trial will be managed at the local District Hospitals in Hung Yen province according to current practice guidelines contained within the educational material for the National Vietnam Hypertension Program. Eligible and consenting patients who meet any one of the criteria outlined in Section 8.1 will be referred for immediate and urgent clinical management: (1) SBP > 180 mmHg; (2) DBP > 120 mmHg; (3) SBP < 90 mmHg; (3) DBP < 60 mmHg; and/or (5) any symptoms suggestive of an acute cardiac process including chest pain, shortness of breath, orthopnea, syncope, or rapid increase in edema or any symptoms suggestive of an neurologic event such as new onset of numbness, tingling, or weakness in the limbs or face, dysarthria, visual disturbance, or vertigo.

9.4 Reporting Procedures

Details of the trial's AE and SAE reporting procedures can be found in the Data Safety Monitoring Plan Document (**Appendix 6**). In brief, the PIs, Drs. Tran, Ha, and Allison, and members of the study team will submit statistical reports to the DSMB at least one week prior to all scheduled meetings. These reports will include all reported data up to and including the 14

days prior to the reporting deadline (except for SAE, which are to be reported within 24 hours of the event). At the beginning of each meeting, the investigators will present a brief overall progress report. This overview will summarize the progress of the trial to date and that there is, or is not, evidence of safety issues that should be addressed by the DSMB. In addition, the report will contain data tables, any changes to the study protocol, recruitment, retention, and tracking of study patients (using a CONSORT diagram), a summary of all AEs and SAEs, baseline measures, and socio-demographic and clinical characteristics of all patients reporting AEs, and any other additional information requested by the DSMB.

9.5 Follow-up for Adverse Events and Serious Adverse Events

Drs. Ha, Tran, and Allison will provide monitoring for all AEs in conjunction with key study personnel. All AEs will be recorded in the research record and any reports of AEs will be reviewed by the PIs or their designees, who are available 24 hours/day. All non-serious AEs will be reviewed during the weekly study meetings. Adverse event documentation will include description of the event, ratings of severity, relationship to study medication/procedures, and follow-up (if any) and related outcomes. All AEs, both serious and non-serious, will be summarized in the required report to the IRB Committee for annual study review and renewal.

The PIs will report to the trial IRB all SAEs that occur in the context of this randomized trial. In general, an SAE is defined as a harmful and undesired effect resulting from a medication or other intervention.

The event is further defined as the following:

- life threatening/results in death OR
- disability/incapacity OR
- requires or prolongs a hospitalization OR
- was otherwise unanticipated, related to the study procedures, or could lead to one of

the other serious event conditions

All AEs and SAEs that occur in the proposed study will be reported to the HSPI's IRB, regardless of whether they are study related or not.

9.6 Safety Monitoring

See Human Subjects Research Document (**Appendix 4**).

10. INTERVENTION DISCONTINUATION

This study is examining the effectiveness of two health strategies which involve a low risk behavioral intervention; therefore, the likelihood of trial discontinuation will be very low. The study may be discontinued at any time by the HSPI's IRB, Vietnam Ministry of Health, and NIH/NHLBI, or other government agencies as part of their duties to ensure that research participants are protected. Participants can withdraw from the study at any time during the study period. A participant will be discontinued from the study if he/she permanently moves out from the province or dies; however, their data will be kept and analyzed at the end of the study and censored at the time of their last available clinic visit.

11. STATISTICAL CONSIDERATIONS

11.1 General Design

Main Hypothesis: At 12 months post-randomization, participants in the intervention group will have a greater mean reduction in their BP levels than those in the comparison group.

This study is a cluster RCT. This design was chosen since the intervention will be implemented at both the community level and patient level. There are 2 trial arms consisting of

an intervention and comparison group. The primary trial outcome is changes in systolic BP from the time of baseline trial enrollment to the 12 month follow-up visit. Secondary outcomes include changes in diastolic BP, changes in HTN control, medication adherence, CVD risk, and cost.

11.2 Sample Size and Randomization

Sample size calculations are based on our primary trial hypothesis with between group differences in over-time changes in systolic BP as the principal trial outcome. Our previous pilot work in rural Vietnam suggests that it feasible to achieve an over-time improvement of 8 mmHg in systolic BP with a standard deviation of 18 mmHg for the observed improvement. Analysis of pilot data revealed an intra-class correlation 0.011 for the clustering of participants in communes for change in systolic BP. We first performed unadjusted sample size calculations that did not account for clustering of individuals within study site and did not inflate for possible loss to follow up. For these calculations, we set alpha error at 0.05 and examined a range of power from 0.8 to 0.9 based on the two-sided t-test with a common standard deviation of 18, assuming that the mean improvement in systolic BP is 8 mmHg for patients in the intervention condition and 3 mmHg for those in the comparison condition.

Next, we adjusted these first-pass sample size calculations to account for the clustering of participants within commune. According to Donner: $N_{adjusted} = N_{undjusted}(1+(m-1)r)$, in which $N_{adjusted}$ is the total sample size adjusted for clustering, $N_{undjusted}$ is the unadjusted total sample size, m is the unadjusted average cluster size (average number of patients/community) and is r the intra-class correlation (ICC)[43]. Finally, we inflated the resulting sample size by approximately 10% to account for potential loss to follow up, which is substantially more conservative than the nearly 100% follow up we in our previous work. It is important to note that the planned analyses for this study will draw upon the power of longitudinal measurement, which will be more powerful than the above-presented estimates[44].

Data to inform these calculations were based on recently published work and are summarized in Table 2. **Based on these considerations, we have set the final recruitment goal at 680 individuals, approximately equally randomized to an intervention and comparison group according to study site.**

In addition to the main analyses described above, we also anticipate adequate power for the planned mediation analysis. For the mediation analysis, simulation studies revealed that a sample size of 500 is adequate to detect pathways with small standardized effect sizes (as low as 0.14) at 80% power with methods described above[45].

Table 2. Sample Size Calculations for Conquering Hypertension in Vietnam: Solutions at Grassroots Level[1]

Power	Sample Size		
	Unadjusted	Cluster-adjusted[2]	Cluster-adjusted and Retention Inflated[3]
0.80	410	522	573
0.85	468	614	**674**
0.90	548	549	823

[1]Sample size calculations assume an improvement in systolic blood pressure of 8 mmHg in the intervention group and 3 mmHg in the comparison group for a differential, over-time improvement of 5 mmHg. Alpha error is set at 0.05
[2]According to approach described by Donner and setting intra-class correlation coefficient at 0.011 based on pilot data.
[3]Final calculations are inflated by approximately 10% to account for potential loss to follow up.

11.3 Description of Masking and Blinding

Due to the nature of the study design, this trial is not masking and not blinding.

11.4 Treatment Assignment Procedures

- Sixteen communes will be randomly assigned to intervention (n=8) or comparison status (n=8) using a computer generated program. Study participants will be assigned to intervention versus comparison status based on the community in which they reside.

The analysis of all trial related data will be based on use of the standard “intent to treat”

approach.

11.5 Interim Analyses and Stopping Rules

An interim analysis will not be performed, and the DSMB will review data for safety and feasibility. The DSMB may make recommendations whether the study the trial will be continued or stopped.

11.5 Study Outcomes

11.5.1 Primary Trial Outcome

Change in patient's systolic BP levels over the 1 year follow-up period is the primary trial outcome. Registered nurses will be trained and certified to measure patient's BP according to a protocol approved by the World Health Organization (**Appendix 4**) and currently implemented by the NIH Coronary Artery Disease In Young Adults (CARDIA) study. The detailed protocol is available at www.cardia.dopm.uab.edu. We referenced this protocol in our previous randomized trial of storytelling (CSI: Birmingham)[30] and in our pilot work in Vietnam. This protocol was written for use with the *OmROn* HEM907XL automated BP monitor, with special attention to assessment and maintenance of the instrument's accuracy and training/certification of research assistants. Using a proper cuff size, measurements of the patient's BP are taken after the patient has been sitting quietly for 5 minutes, with the arm supported on a flat surface, with the upper arm at heart level. The patient's back will be supported, and both feet should be flat on the floor. Three measurements of BP will be separated by at least one minute, and values from the last two measurements will be averaged with the first reading ignored.

11.5.2 Secondary Trial Outcomes

Changes in diastolic BP, HTN control, risk factors for CVD, medication adherence, self-efficacy, quality of life, cost, and implementation outcomes (section 11.5.3) are secondary

outcomes of this study. The WHO STEPs survey, which has been used to investigate the epidemiology of HTN in the Vietnamese language,[32] will be used to collect data on risk factors for CVD including tobacco use, alcohol consumption, salt intake, and physical activity. Medication adherence will be collected using the form that was developed by the investigators at Duke University[26]. Patient's self- efficacy will be measured by Medication Adherence Self-efficacy Scale (MASES) instrument[27,28]. Quality of life will be measured by the short form 12 questionnaire health survey (SF-12)[29]. Costs include: (1) program costs, which consist of costs to develop the intervention and implementation costs incurred at the district and community levels; and (2) patient costs such as drugs, diagnostic procedures, time lost, health center visits, and consultation fees.

11.5.3 Implementation Outcomes

The information on intervention acceptability, appropriateness, and feasibility will be collected via:

- Semi-structured interviews and focus group discussions among stakeholders and patients mentioned previous (Qualitative studies- Section 3).
- Patient's interviews and post-DVD viewing surveys at follow up visits (Data collection- Section 8.1).
- The intervention fidelity will be collected via observation of the PIs and the project manager.

With regards to intervention adoption, data for participant recruitment and retention will include the number of patients approached for recruitment, reasons for ineligibility of patients not enrolled or refusing to participate, and completion rates for follow-up visits. Data collected for intervention delivery will include number of BP self-monitoring devices given to participants, use of self-monitoring BP devices as documented by patient's logs brought in to clinic visits, and

the number and types of educational materials provided. We will ascertain changes made to the clinic structure to accommodate the expanded CHW role, implementation of the standardized BP measurement protocol, and number and types of educational sessions attended by the physicians and nurses at participating clinics (qualitative interviews described in Section 3).

The implementation data and barriers to study milestones achievement gathered by the research team will inform strategies to overcome barriers and progress toward specific study milestones.

11.6 Data Analyses

We will begin the statistical analysis by examining univariate statistics, including measures of central tendency and dispersion, such as the mean and standard deviation for data that approximate a normal distribution or the median and inter-quartile range for skewed data. We will carefully document the trial recruitment and retention process with a CONSORT diagram[46,47].In accordance with best practice, differences in baseline characteristics of the intervention and comparison groups will be established based on standardized differences, rather than on tests of statistical significance.[48,49] All primary hypothesis testing will be performed on an intent-to-treat basis and be two-sided with alpha error will be set at 0.05.

For the main study hypothesis, the continuous outcomes will be systolic (H1) and diastolic (H2) BP. We will parameterize a generalized linear mixed model, as specified below:

i: subject index

j: commune index

t: time (0,3,6,12)

Y: SBP

T_j: randomized treatment group (0 or 1)

β_t: parameter for time=t

θ_t: parameter for treatment=1 at time=t (t >0)

a_j: random commune effect ~ N(mean=0)

b_i: random subject effect ~ N(mean=0)

ε_{ijt}: random error term ~ N(mean=0)

I(): indicator of event specified in brackets()

$$Y_{ijt} = a_j + b_i + \beta_t + \theta_t I(T_j=1, t>0) + \varepsilon_{ijt}$$

Based on this model, the treatment effect will be given by θ_{12}. Additional baseline covariates that will be included in the model are baseline blood pressure value and age.

Secondary analyses will adjust for important potential covariate imbalances between the 2 primary study comparison groups.

As we will collect longitudinal data with repeated observations nested within participant, and participants nested within commune, many statistical analyses will be based on a generalized linear mixed model with Restricted Maximum Likelihood (REML) estimation that accounts for the complex data structure through random effects and uses appropriate link functions for various distributions of the response variable.[50-53] The most general structure of the mixed model may be written as $\mathbf{y} = \mathbf{X\beta} + \mathbf{Z\gamma} + \boldsymbol{\varepsilon}$, where the $\mathbf{y}$ matrix represents the observed outcomes, $\boldsymbol{\beta}$ is a vector of fixed-effect parameters with a design matrix $\mathbf{X}$, $\boldsymbol{\gamma}$ is a vector of random-effect parameters with design matrix $\mathbf{Z}$, and $\boldsymbol{\varepsilon}$ is a random-error vector.[54,55] We will assume that $\boldsymbol{\gamma}$ has a multivariable normal distribution with mean 0, and that it is independent of $\boldsymbol{\varepsilon}$. We will examine residuals to look for gross violations of the underlying assumptions, and explore various approaches to address identified violations such as variable transformation, outlier trimming, or placing bounds on the extent to which extreme observations affect any trial related conclusions.

We will use mediation analysis to disentangle the multiple mechanisms which may be associated with the effectiveness of our multi-level intervention. Patient-level mediators of

intervention effectiveness include: (1) intervention engagement (measured by number of CHW sessions completed and time spent in the sessions, types of goals set and corresponding action plans, BP self-monitoring, engagement with the storytelling intervention as documented by the post-media interviews such as the number of minutes viewing the DVDs at home); (2) medication adherence; (3) adherence to heart-healthy lifestyle recommendations; and (4) patient activation. Clinic-level mediators include implementation of standardized BP measurement protocols; engagement of physicians and nurses in the trial educational programs; fidelity of CHW intervention delivery; and implementation of the clinical software.

Mediation analyses will draw upon classic principles modified from Barron and Kenny[56] and will be implemented with Structural Equation Modeling[57-60], allowing for the simultaneous estimation of multiple regression equations representing complex mediation pathways with correlated errors. Mediation ratios will quantify the proportion of the intervention effect transmitted through a given pathway, with 95% bias-corrected confidence intervals from bootstrapped re-sampling with replacement[61,62].

For the secondary analysis, we will examine differential over-time changes in diastolic BP, HTN control, and CVD risk, using statistical approaches described above for testing the main study hypothesis. For these analyses, a dichotomous measure of BP control will be constructed according to JNC-8. Overall risk of a CVD event at 10 years will be calculated based on the Asian Pacific Cohort equation, which is based on age, sex, systolic blood pressure, and total cholesterol[63], and which has been validated in a rural region of Vietnam[64]. The Framingham general risk score, which also includes variables for diabetes and HTN control, is often considered to be the gold standard[65], but it has come under scrutiny recently for not being representative of diverse populations and over-estimating risk in Asian populations[66,67]. However, we will also calculate the Framingham score for comparison with data reported in the largest national study of CVD risk in Vietnam[68]. We will examine changes in

patient's individual risk factors for CVD (e.g., smoking, physical inactivity) as well. We will examine for possible heterogeneity of intervention effect among sub-groups of participants defined by age, sex, and existing CVD. These sub-group analyses are exploratory and may lack power because of small cell sizes. Therefore, based on arguments by Rothman, we will forego adjustment for multiple comparisons for the planned sub-group analyses[69].

The economic analysis will be led by Dr. Ha, who has expertise in evaluating the cost effectiveness of interventions to prevent CVD in Vietnam[70]. From the societal perspective, we will analyze costs and effectiveness for the intervention package with the proposed enhancements in comparison to standard implementation of the Vietnam National HTN Program, using approaches appropriate for lower-to-middle income countries[71,72]. Costs include: (1) program costs, which consist of costs to develop the intervention and implementation costs incurred at the district and community levels; and (2) patient costs such as drugs, diagnostic procedures, time lost, health center visits, and consultation fees. We will calculate the incremental costs of the intervention by subtracting the average costs for the intervention group from the average costs for the comparison group. The incremental cost-effectiveness ratio will calculated as the additional cost of the intervention divided by the change in both systolic and diastolic BP related to the intervention. In addition, we will calculate cost-effectiveness ratios for BP control, by dividing the additional costs of the intervention by the proportion who achieved HTN control as a result of the intervention. Because this is a country-specific economic analysis, all costs will be evaluated using the Vietnamese Dong (VND) with subsequent conversion to US dollars. We will perform one-way sensitivity analyses related to variable intervention effectiveness, variable engagement, and trial adherence. Finally, for the multi-way sensitivity analysis we will examine best-case and worst-case scenarios using lower health effect limits and highest drug prices (worst-case), and upper health effect limits and lowest drug prices (best-case).

12. PARTICIPANT RIGHTS AND CONFIDENTIALITY

12.1 Institutional Review Board (IRB) Review

The protocol including the Data Safety and Monitoring Plan (Appendix 5), and the informed consent document (Appendix 7), and any subsequent modifications, will be reviewed and approved by the HSPI IRB, who are responsible for oversight of the study.

12.2 Informed Consent Forms

Trained study staff will be responsible for obtaining written and signed informed consent forms from each patient (Appendix 7). The consent forms will describe the purpose of the study, the procedures to be followed, and the risks and benefits of study participation. A copy will be given to each participant, which will be documented in the patient's medical record.

Although physicians, nurses, clinic personnel, and all CHWs will undergo training as part of the trial, they will not participate as research subjects, and, therefore, will not provide informed consent. No personal information will be collected from these individuals. However, they will have the right to refuse participation in the educational activities without adverse consequences.

12.3 Participant Confidentiality

Any data collection forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain complete confidentiality. All records will be kept in a locked file cabinet during the study period and for 10 years after study completion and destroyed according to the standard protocol at HSPI. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by HSPI's IRB, Vietnam Ministry of Health, and NIH/NHLBI.

13. STUDY TIMELINE

Our study will be a two-arm cluster randomized trial which focuses on rigorously testing the intervention and collecting secondary data about the implementation process[73,74]. First, there will be a needs assessment to guide the formative work and intervention refinement. The Vietnam National HTN Program will be implemented for both intervention and comparison groups. The intervention group only will also receive three carefully selected enhancements based on our conceptual models to both empower patients and promote patient-provider collaboration in improving HTN control. Both study groups will receive implementation assistance. All intervention enhancements will be made available to the comparison group at the conclusion of the study.

Sixteen communes, with a total of 680 adult patients with uncontrolled HTN, will be randomized to an intervention (n=8) or comparison group (n=8). All participants in both study groups will have their BP measured with standardized protocols at baseline and at 3, 6, and 12 months after trial enrollment.

Figure 2. Study timeline (updated)

Year	Year 1				Year 2				Year 3				Year 4				Year 5			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Conduct needs assessment																				
Develop intervention enhancements																				
Training for intervention delivery																				
Screen and recruit participants																				
Implement intervention																				
Collect survey, blood pressure data																				
Review medical records																				
Collect qualitative data																				
Analyze data from trial																				
Prepare manuscripts and reports																				

14. COMMITTEES

14.1 Steering Committee

Vietnam team:

Oanh Tran, MD, Ph.D, Chair

Duc Ha, MD, MS, DrPH: Co-Chair

Van Phan, MD, Ph.D

Tuan Nguyen, MD, Ph.D

Bac Truong, MD, Ph.D

Linh Vuong, BS

US team:

Jeroan Allison, MD, MS: Co-Chair

Robert Goldberg, Ph.D

Hoa Nguyen, MD, MS, Ph.D

Sharina Person, Ph.D

Germán Chiriboga, MPH

Brad Newsome, Ph.D

14.2 Publication Committee

Robert Goldberg, Ph.D: Chair

Jeroan Allison, MD, MS: Co-Chair

Duc Ha, MD, MS, DrPH: Co-Chair

Oanh Tran, MD, Ph.D

Hoa Nguyen, MD, MS, Ph.D

Sharina Person, Ph.D

Germán Chiriboga, MPH

Van Phan, MD, Ph.D

Tuan Nguyen, MD, Ph.D

Bac Truong, MD, Ph.D

15. PUBLICATION OF RESEARCH FINDINGS

NA

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17. SUPPLEMENTS/APPENDICES

Appendix 1. List of participating and back up communes and characteristics

Appendix 2: Hypertension Control Program Training Materials

Appendix 3: Blood Pressure Log

Appendix 4: Data collection forms, instructions and Manual of Operation.

Appendix 5: Human Subject Protection

Appendix 6: Data Safety Monitoring Plan

Appendix 7: Informed consent forms