Trial Design

# Rationale and design of a cluster randomized trial of a multifaceted intervention in people with hypertension: The Heart Outcomes Prevention and Evaluation 4 (HOPE-4) Study

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## ARTICLE INFO

## ABSTRACT

*Background:* Cardiovascular disease is the leading cause of death throughout the world, with the majority of deaths occurring in low- and middle-income countries. Despite clear evidence for the benefits of blood pressure reduction and availability of safe and low-cost medications, most individuals are either unaware of their condition or not adequately treated.

*Objective:* The primary objective of this study is to evaluate whether a community-based, multifaceted intervention package primarily provided by nonphysician health workers can improve long-term cardiovascular risk in people with hypertension by addressing identified barriers at the patient, health care provider, and health system levels.

*Methods/design:* HOPE-4 is a community-based, parallel-group, cluster randomized controlled trial involving 30 communities (1,376 participants) in Colombia and Malaysia. Participants ≥50 years old and with newly diagnosed or poorly controlled hypertension were included. Communities were randomized to usual care or to a multifaceted intervention package that entails (1) detection, treatment, and control of cardiovascular risk factors by nonphysician health workers in the community, who use tablet-based simplified management algorithms, decision support, and counseling programs; (2) free dispensation of combination antihypertensive and cholesterol-lowering medications, supervised by local physicians; and (3) support from a participant-nominated treatment supporter (either a friend or family member). The primary outcome is the change in Framingham Risk Score after 12 months between the intervention and control communities. Secondary outcomes including change in blood pressure, lipid levels, and Interheart Risk Score will be evaluated.

*Significance:* If successful, the study could serve as a model to develop low-cost, effective, and scalable strategies to reduce cardiovascular risk in people with hypertension.

## Background

Cardiovascular disease (CVD) is the major cause of mortality and morbidity globally and affects half of all individuals over their lifetimes.[1] Despite large reductions in age-adjusted mortality in many high-

**Table I**

Rationale and approach to intervention design in the HOPE-4 Program (adapted from Schwalm et al 2016 *Circulation* article titled "Resource Effective Strategies to Prevent and Treat Cardiovascular Disease")[43]

| Category of barrier | Example of barrier | Strategies in HOPE-4 |
|---|---|---|
| **Patient[7]** | | |
| Availability, access, and costs of medication and health care (external) | Lack of health insurance (public or private) | (1) Free medication, (2) NPHWs, (3) medication delivery at the community level |
| Knowledge (internal) | Asymptomatic individuals question need for ongoing treatment | (1) NPHW-initiated education/counseling, with mhealth support; (2) treatment supporters |
| Beliefs (internal) | Alternative/traditional medicine | NPHW-initiated education to address beliefs that impair acceptance of evidence-based messages |
| Memory (internal) | Affects adherence to recommended therapies and attendance to HCP follow-up | NPHW-initiated visits with participant (at least 6 total visits in 12 m), (2) treatment supporters to promote and encourage adherence |
| Adverse effects of medications (internal) | Real or perceived (myalgia, cough, etc) | (1) NPHW assessment, scheduling of HCP-participant appointment if necessary, and education; (2) use of low-dose combination medications to minimize adverse effects |
| **Health care provider[7, 41]** | | |
| Knowledge | Familiarity and awareness of management options and guidelines | HOPE-4 simplified treatment algorithm using evidence-based recommendations |
| Attitudes | Lack of agreement on guidelines, expectations, self-efficacy, motivation, and treatment inertia | (1) Simplified algorithms, informed by evidence-based recommendations, packaged into a treatment manual; (2) participant risk and treatment recommendations suggested by NPHWs, with mhealth support |
| Behavior | External or environmental factors limiting management (time, resources, reimbursement) | Task-shifting responsibilities to NPHWs, with mhealth support |
| **Health system/policy[42]** | | |
| Health care financing system | Low priority in national budgets: competing political agendas (military, other medical conditions such as HIV, etc); limited universal health care coverage | Partner with national health care leaders in Colombia and Malaysia |
| Medical products and technologies | Lacking infrastructures for stocking pharmacies with evidence-based generic medications; poor affordability of essential medications, even when they are generic | Combination of purchased and locally donated combination CV medications stocked and provided to participants |
| Leadership/governance | Low priority for CVD prevention: lack of effective screening programs, smoking cessation programs, safe environments for exercise, high costs for healthy foods, lack of physical activity | (1) Simplified treatment and management algorithms, with mhealth support. This includes simple and achievable recommendations for lifestyle changes. (2) Treatment supporters add layer of support |
| Health workforce | Limited number of adequately trained physicians and health care professionals | Task-shifting responsibilities to NPHWs supported by mhealth technology |
| Health information system and research | Limited health system infrastructures to ensure monitoring of health determinants, performance and health status | mhealth tablets provide data management support |
| Service delivery | Efficient delivery of effective and safe interventions | Task-shifting of responsibilities to NPHWs at the community level, with mhealth support and HCP supervision |

HCP, Health care provider.

income countries (HICs), rates are now increasing in many low- and middle-income countries (LMICs).[2] In 2015, >75% of noncommunicable disease deaths occurred in LMICs, with CVD as the leading cause (17.7 million deaths, or 45% of all noncommunicable disease deaths).[3] Smoking, hyperlipidemia, hypertension, and diabetes account for 80% of the population attributable risk for CVD, with hypertension fast becoming the main driver of CVD.[4] Early detection of these modifiable cardiovascular (CV) risk factors followed by initiation of and adherence to existing evidence-based CV medications and lifestyle modifications can substantially reduce CVD risk.[5, 6]

The Heart Outcomes Prevention and Evaluation 4 (HOPE-4) community-based program in Malaysia and Colombia was informed by an extensive analysis which included a systematic review of barriers to effective hypertension management coupled with 2 in-depth mixed-methods situation analyses in each country.[7-9] These identified context-specific factors, such as traditional health beliefs in Malaysia and fragmentation of provision of care in Colombia, and informed development of a contextually appropriate multifaceted intervention package for CVD prevention in each country. We are testing this intervention package in a community-based, parallel-group, cluster randomized controlled trial.

Substantial gaps in the detection, treatment, and control of CVD risk factors occur globally, especially in LMICs.[10-14] Barriers to CVD prevention occur at 3 levels: patient, health care provider, and health system levels (Table I).[7, 8, 15-17] To overcome barriers at all these levels, we have integrated the following 3 complementary approaches: (1) task-shifting to teams of nonphysician health workers (NPHWs), supported by mobile health (mhealth) tablets for decision support counseling and data collection; (2) combination antihypertensive (anti-HT) and cholesterol-lowering medications provided to eligible participants; and (3) involvement of participant-nominated treatment supporters to optimize long-term adherence to medications and healthy lifestyle.

I. Task-shifting, supported by tablet-operated, mhealth systems: Detection of hypertension, documentation of risk factors, lifestyle counseling, and reinforcement of adherence to prescribed medications can be done efficiently by community-based NPHWs.[18] However, in most countries, prescribing drugs is only permitted by licensed physicians. Therefore, the World Health Organization (WHO) recommends a combined approach whereby NPHWs identify individuals with hypertension/CVD risk and physicians prescribe proven drugs following established guidelines. Such an approach is particularly relevant in resource-challenged settings where there are an inadequate number of physicians.[19-24] Most screening guidelines for hypertension emphasize the need for multiple readings of elevated blood pressure (BP) before initiating treatment.[25-28] However, these guidelines are based on experiences in HICs with ample human and financial resources and have never been validated as being cost-effective or practical from the patient perspective. The need to make multiple visits to document whether or not BP is elevated is often a barrier to initiation of anti-HT therapies.[10] We hypothesize that simplified

**Table II**
Community characteristics by country and urban or rural settings

| Characteristics | Malaysia | | Colombia | |
| --- | --- | --- | --- | --- |
| | Rural<br>8 clusters; n=341 | Urban<br>7 clusters; n=275 | Rural<br>6 clusters; n=307 | Urban<br>9 clusters; n=453 |
| Mean distance (km) between community and coordination center | 103.2<br>(SD 64.6) | 35.2<br>(SD 23.2) | 98.8<br>(SD 121.8) | 42.8<br>(SD 51.6) |
| Mean population (n) | 12,873.5<br>(SD 9778.5) | 197,451<br>(SD 156,921.7) | 22,188.5<br>(SD 15,622.1) | 12,087.9<br>(SD 15,192.9) |
| Male (%) | 51.4 | 53.2 | 51.7 | 49.1 |
| Age ≥50 (%) | 25.6 | 21.1 | 26.0 | 27.8 |
| Storage of medication | Locally stored | Locally stored | Centrally stored | Centrally stored |
| Mean no. of government or private clinics (n) | 4.8<br>(SD 2.4) | 19.0<br>(SD 7.7) | 1.2<br>(SD 1.0) | 2.7<br>(SD 3.9) |
| Mean no. of hospitals (n) | 1.1<br>(SD 0.4) | 3.3<br>(SD 1.6) | 0.8<br>(SD 0.4) | 0.9<br>(SD 0.3) |
| Mean no. of tertiary care centers (n) | 0 | 0.6<br>(SD 0.8) | 0.2<br>(SD 0.4) | 0.7<br>(SD 0.5) |
| Mean no. of specialist centers (n) | 0 | 0.3<br>(SD 0.5) | 0<br>(SD 0) | 0<br>(SD 0) |
| Primary settings for recruitment data collection | 99% from public community centers; 1% from private households | 75% from public community centers; 25% from private households | 100% from private households | 100% from private households |

approaches to initiate anti-HT drugs with only 1 or 2 BP measurements while simultaneously taking measures to reduce lipids and modify other risk factors could reduce the risk of CVD in those at high risk. Such approaches can now benefit from advances in computerized decision support systems.[29-33] Thus, we integrated these algorithms into the HOPE-4 tablet-based mhealth systems.

II. Use of free combination of anti-HT and cholesterol-lowering medications:

Because no single drug reduces BP sufficiently in most people with hypertension, BP control is better achieved using combinations of low doses of anti-HT agents, an approach endorsed by both European and US guidelines.[27, 34] Given recent evidence supporting the use of statins in those with hypertension, regardless of lipid status, this medication is also recommended for eligible participants.[35-38] High medication cost and limited availability have been identified as a barrier to effective hypertension management.[39] Consequently, the HOPE-4 program provided these drugs at no cost in each country.

III. Treatment supporters:

Experience with HIV treatment has demonstrated that involvement of uncompensated, participant-nominated friends or family significantly improved treatment adherence and reduced mortality.[40] Given similarities across chronic disease management strategies, involving treatment supporters may also be an effective approach to CVD management.

## Research methods

### Objectives

The goal of the HOPE-4 study is to evaluate an evidence-based, contextually appropriate program for CVD risk assessment, treatment, and control involving the 3 elements set out above.

### Study design

Using a parallel-group, cluster randomized controlled trial design, 30 communities have been randomized to usual care or to participate in an intensive CVD risk detection and management program supported by NPHWs for 12 months. Participants, NPHWs and local investigators will not be blinded to the study group. Data collected will be transferred to the Population Health Research Institute (PHRI) directly from the tablets for analysis. This protocol is registered on www.clinicaltrials.gov (identifier NCT01826019).

### Study population

#### Selection of communities

The study coordinating center and the national leaders in each country have collaborated to develop country-specific definitions for urban and rural communities and to identify the households to be screened within each community. Use of a Community Characteristic Checklist (Table II) to capture community demographics and health care facilities information formalized the community selection process and facilitated reporting that is in line with the Consolidated Standards of Reporting Trials guidelines.[44] Essentially, the communities were selected to minimize the risk of contamination between clusters (ie, participants from one community are not likely to visit the health care center in another community). This trial has randomized 30 urban and rural communities in Colombia (registration site: FOSCAL) and Malaysia (registration site: Universiti Teknologi MARA).

#### Participant selection

Screening to identify eligible participants involved a combination of household sampling and the use of community outreach centers or events based within public spaces, as appropriate to the region. For this screening, medical clinics (ie, primary care physician offices or hypertension clinics) were purposely avoided. Participants were considered eligible if they were ≥50 years old with at least **ONE** of the following criteria:

1. Systolic blood pressure (SBP) ≥160 mm Hg was recorded at 1 visit;
2. SBP 140-159 mm Hg was recorded in 1 visit AND participant reported a medical diagnosis of hypertension or was taking anti-HT medication;
3. SBP ≥130 mm Hg was recorded in 1 visit AND participant reported a medical diagnosis of diabetes or was taking medication for diabetes;
4. Participants did not meet criteria 1-3, but SBP 140-159 mm Hg was recorded on 2 separate visits at least 24 hours apart.

Participants were considered ineligible for this study if they (1) refused to consent, (2) were concurrently participating in any other study or heart health program that would compromise the protocol of HOPE-4, (3) had severe comorbid condition with life expectancy <1 year, or (4) had other serious condition(s) or factors likely to interfere with study participation or with their ability to complete the trial (see Figure 1 for the enrollment process).
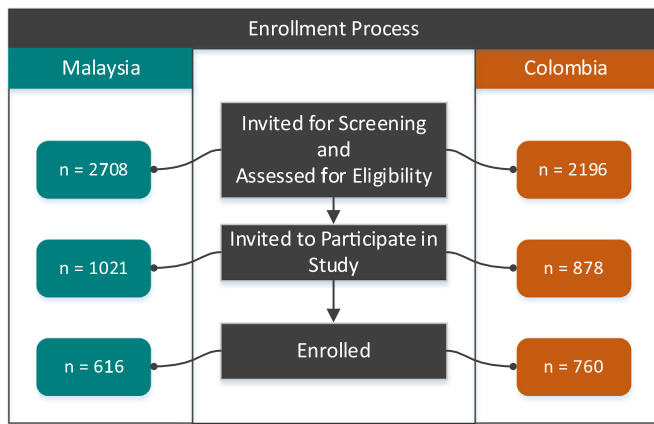
**Figure 1.** Flowchart of the participant enrollment process.

*Informed consent*

All participants ≥50 years old were asked to sign a short informed screening consent form prior to completion of medical history screening questions and BP assessment to determine study eligibility (Appendix A). Participants who wish to participate in the trial must sign an informed enrollment consent form (Appendix B). This consent can occur at the same visit immediately after the completion of initial screening or in the targeted 14-day follow-up period after initial screening, depending on the results of screening and number of visits required to establish eligibility.

*Randomization*

Following screening and complete participant enrollment within a given community, communities were randomized 1:1 by a computer-generated, central (PHRI) randomization system to either the intervention or control group. Each community was randomized after the entire community was screened to avoid selection bias. This strategy limits biases regarding which participants would be included in the trial before randomization within each community. All participants within the defined community will receive the allocated treatment. Stratified randomization was first by country and then by rural or urban location of the community. Rural/urban stratification was undertaken, as there are marked differences in the use of secondary preventative medications and in hypertension control between these settings as documented in the Prospective Urban and Rural Epidemiological (PURE) study, which is being undertaken in both countries.[10, 14]

*Intervention components*

This cluster randomized controlled trial involves a complex intervention consisting of 3 core elements (Figure 2) provided as a package: (1) task-shifting to NPHWs, (2) dispensing combination anti-HT and cholesterol-lowering medications and reinforcing adherence, and (3) involvement of participant-nominated treatment supporters to encourage adherence, adapted to the local context.

*Task-shifting*

A curriculum for training of NPHWs was jointly developed by PHRI and the WHO with 9 modules of instructions.[23, 45] In this 2-week curriculum, NPHWs were trained on a variety of topics ranging from common CV health knowledge to CV risk detection, treatment, and lifestyle management. NPHWs were also trained to counsel both the study participants and their nominated treatment supporters on the benefits of adherence to medication and adoption of healthy living (eg, diet,

exercise, and smoking cessation). These are reiterated with each NPHW-participant contact. Local primary health care physicians will review decisions made by the NPHW, as well as initiate simplified algorithms for medication dispensation where appropriate.

To further promote task-shifting of responsibilities to NPHWs, tablets with HOPE-4 software were developed and provided to all NPHWs. To support decisions, counseling, and data collection, tablets were programmed with simplified clinical algorithms, NPHW counseling prompts, and study management instructions, all based on the study protocol and the curriculum developed for the NPHWs. The tablets were validated and tested before distribution.[46] Using branching logic and decision trees, the tablets specifically provide NPHWs with (1) step-by-step screening assessments; (2) secure electronic data capture and transfer; (3) progress indicators on the status of each participant, describing completeness of data collection; and (4) real-time decision support and feedback for both participant guidance and data validation. Similar to other computer decision-support systems, the tablet offers the ability to use preprogrammed clinical knowledge so that recommendations can be made once characteristics of the participant are entered, based on expert physician knowledge, guidelines, and the standardized WHO/package of essential noncommunicable disease protocols.[47]

*Administration of study medications*

Study-associated medications are obtained from a local manufacturer within each country. Although the precise formulations used differ in each country, the recommended CV medications include single-pill combinations of anti-HT medications (both low- and high-dose options) and a cholesterol-lowering agent (statin) (Table III). Initiation of medication options from Table III is based on recommendations from the NPHW, but the ultimate decision is left to the discretion of the participating local physician, depending on (1) the communities' medication availability and the participant's (2) BP, (3) risk profile, and (4) allergies/medication intolerances. Eligible participants already taking CV medication(s) are reviewed by the NPHW and supervising physician for potential transition (if appropriate) to the study-associated medications in accordance with local policy and guidelines, but this is not mandatory. Participating NPHWs and physicians have been provided with suggested medication management algorithms tailored to available study-associated medications (Figure 3).

*Safety reporting*

Safety reporting will be customized for each region, country, and the regulatory status and type of study-associated medication provided and used, as appropriate, and as required by regulatory authorities within participating countries. If study-associated medication (ie, medication obtained centrally and provided free of charge to participating intervention communities) is not provided to a given region or country as part of HOPE-4, it is expected that no medication-related safety reporting will be required, in accordance with local regulations. It is also expected that medication-related safety reporting will not be required for control communities, in accordance with local regulations. Any participants experiencing adverse effects or uncontrolled HT within the intervention group will be managed by study physicians as per local policy and guidelines. Participants who develop intolerable adverse effects to a component of any study-associated medication may be transitioned to a more suitable study-associated medication or to its individual components or other suitable medications, if available, in accordance with local policy and guidelines.

These algorithms will prioritize the use of combined anti-HT and cholesterol-lowering medications in tolerant participants. Any participant experiencing adverse effects or uncontrolled hypertension will be managed by local health care providers as per local policy and guidelines.
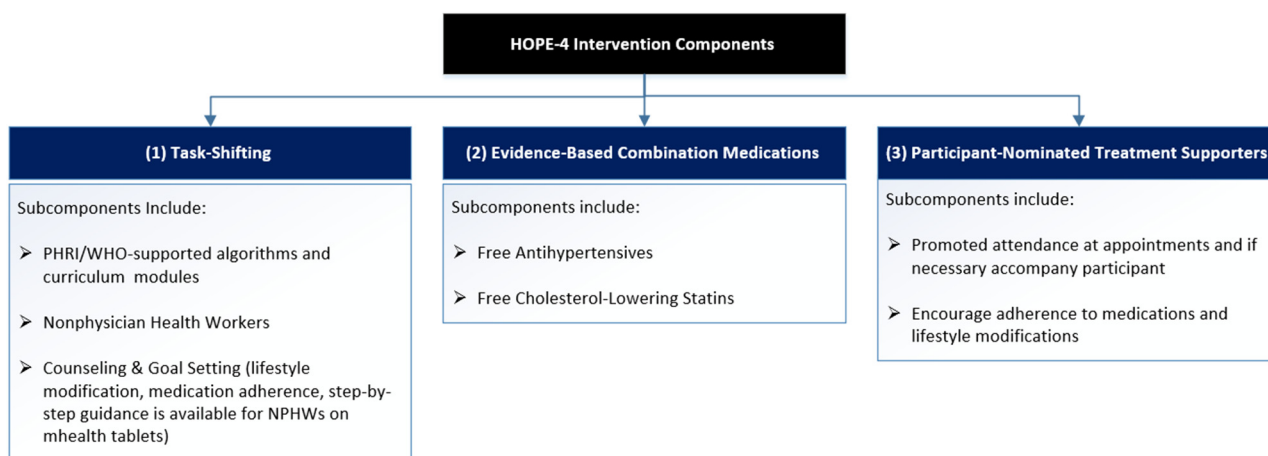
**Figure 2.** Intervention components of HOPE-4.

*Control*

No structured interventions will be used in the control arm. During screening, control participants will be provided with existing government/health system CVD literature and be advised to see their usual provider for care, as appropriate. Treatments prescribed are recorded in each participant.

*Study visits and data collection*

Study visits and data collection will be conducted by trained NPHWs, who will travel to the participants' homes or community outreach centers within preselected communities (see Table II for the Community Characteristic Checklist used to select communities). At prerandomization screening, NPHWs will assess each consenting individual aged 50 years or older and collect physical measurements to determine study eligibility. At 6 and 12 months postrandomization in intervention and control communities, NPHWs will repeat study assessment procedures to ensure that any changes to the components of Framingham Risk Score (FRS) are captured. Blood work will be collected in participants at baseline and 12 months (low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total cholesterol, and glucose). Blood pressures are taken at each visit using the WHO STEPS Protocol.[48]

Communities randomized to intervention will have additional visits, which include a baseline visit (time-0 visit; a participant-NPHW visit, and a participant-physician visit) at 1 and 3 months postbaseline. An additional telephone call will be made to intervention participants at 10 or 11 months to confirm availability for the upcoming 12-month visit. Communities randomized to control will have no additional visits—only a telephone call at 3 months and at 10 or 11 months to confirm upcoming visits with the NPHW.

Data will usually be collected using tablets; however, NPHWs can choose to capture data on paper forms for later entry if necessary depending on the participant and setting.

Figure 4 shows a summary of the NPHW management responsibilities in intervention and control groups.

*Outcomes*

The complex HOPE-4 intervention is designed to address CVD risk by improving BP and lipid control and promoting smoking cessation as well as other lifestyle modifications. Therefore, a validated risk score assessing the major modifiable CVD risk factors is required to properly evaluate the effect of HOPE-4 interventions. The FRS is a tool to estimate the risk of CVD development based on age, sex, BP, use of anti-HT

medication, blood cholesterol, smoking, and diabetes. The FRS was initially developed in white Americans but has subsequently been widely validated in different ethnic groups.[49, 50] The primary objective of HOPE-4 is to evaluate whether or not the intervention can substantially improve the FRS at 1 year. Given the potential for detection bias (increased screening in the intervention group), the development of a new diagnosis of diabetes after the initial screening assessment will not factor into the FRS calculation at 12 months. We expect that HOPE-4 will also have an 80% power to detect small changes in BP (≥2.9 mm Hg) and LDL cholesterol (≥0.67 mmol/L), as secondary outcomes.

*Primary outcome*

The primary outcome is the mean difference in FRS change from baseline to 12 months between the intervention and control communities. The FRS will be calculated using lipid measurements, but if they are missing, a nonlaboratory FRS validated formula will be used.[51] Although the HOPE-4 study initially planned to assess change in SBP as the primary outcome, it was felt that this outcome did not reflect the multifaceted nature of the intervention. This study is well powered for both FRS and SBP as outcomes of interest.

*Secondary outcomes*

The secondary outcomes are (1) change in SBP between the intervention and control communities at 6 and 12 months; (2) change in LDL, HDL, total cholesterol, triglycerides, and glucose levels at 12 months; (3) proportion of participants with well-controlled BP at 6 and 12 months (SBP < 140 mm Hg); (4) change in smoking status at 6 and 12 months.

*Tertiary outcomes*

The tertiary outcomes are (1) change in Interheart Risk Score at 6 and 12 months and Cholesterol Modifiable Risk Score at 12 months, (2) change in lifestyle modification (exercise and diet-based on components of the Interheart Risk Score), (3) proportion of participants receiving 2 or more anti-HT and a statin at 6 and 12 months, (4) medication adherence measures at 6 and 12 months, (5) country-specific process outcomes at 6 and 12 months involved in the intervention, and (6) health economic analyses.

*Safety outcomes*

The safety outcomes are clinical events (eg, death, CVD development, hospitalizations) at 6 and 12 months. However, given the modest sample size and relatively short duration of the intervention, the study will not have high power to detect differences in these outcomes.

**Table III**
Combination anti-HT study medications dispensed in Malaysia and Colombia

| Malaysia[*] | | | Colombia[*] | | |
|---|---|---|---|---|---|
| Anti-HT medications | Doses | | Anti-HT medications | Doses | |
| Options: low-dose combinations | | | Options: low-dose combinations | | |
| 1 | Perindopril | 4 mg | 1 | Amlodipine | 5 mg |
| | Indapamide | 1.25 mg | | Valsartan | 80 mg |
| 2 | Telmisartan | 80 mg | 2 | Candesartan | 16 mg |
| | Amlodipine | 5 mg | | Amlodipine | 5 mg |
| Options: high-dose combinations | | | Options: high-dose combinations | | |
| **1** | Telmisartan | 80 mg | **1** | Amlodipine | 10 mg |
| | Amlodipine | 10 mg | | Valsartan | 160 mg |
| **2** | Amlodipine | 5 mg | **2** | Amlodipine | 5 mg |
| | Valsartan | 80 mg | | Valsartan | 160 mg |
| **3** | Amlodipine | 5 mg | | Hydrochlorothiazide | 12.5 mg |
| | Valsartan | 160 mg | **3** | Candesartan | 32 mg |
| | | | | Amlodipine | 5 mg |

* Atorvastatin 20 mg or rosuvastatin 10 mg also provided to eligible participants.

## Statistical considerations

### Sample size

Sample size calculations used data from participants enrolled in the PURE study from Malaysia and Colombia.[52, 53] HOPE-4 participants are expected to be similar to the PURE study population. Among the 2,832 PURE participants from Malaysia and Colombia that met HOPE-4 eligibility, the mean baseline FRS score was 24.7% (SD 15). The mean SBP is 160 (SD 19) and LDL cholesterol is 3.58 mmol/L (SD 1.09). The community intraclass correlation coefficients (ICCs) for FRS, SBP, and LDL cholesterol were 0.052, 0.017, and 0.11, respectively. We set a sample size of 1,200 across the 2 groups (30 clusters with 40 each in size; 600 in the intervention and 600 in the control group). Based on these assumptions, we will have 80% power to detect at least 3.0% absolute FRS percentage points difference in FRS between intervention and control group. Similarly, for our secondary outcomes, we will have 80% power to detect a 2.9–mm Hg difference in BP and a 0.32-mmol/L difference in LDL between these 2 groups (Tables IV and V).

### Analyses

Analysis and reporting of results will follow the Consolidated Standards of Reporting Trials guidelines for cluster randomized controlled trials.[54] The analysis of both primary and secondary outcomes will account for the clustering effect using mixed-effects model with community as a random effect. We will use multiple imputation strategies based on the baseline characteristics to take into account missing data on all outcomes. We will undertake an intention-to-treat analysis.[55]

All statistical tests will be performed using 2-sided tests at the .05 level of significance. Final results will be expressed as a mean along with 2-sided 95% CIs and P values. The consistency of treatment effects on the primary outcome will be explored in predefined subgroups, including socioeconomic status, education, gender, country, urban/rural community, and young/old, and by risk score tertile. Tests for interactions of subgroups with the intervention will be performed by including an interaction term in the model. These subgroup analyses will not be adjusted for multiple testing because the analyses are exploratory.

We will perform the following sensitivity analyses for the primary outcome, altering the model for analysis of cluster randomized controlled trials.[56] First, we will use a generalized estimating equation, assuming an exchangeable correlation structure within each community.[57] We will also use:(1) random-effects patient-level analysis methods and cluster-level (ie, random- and fixed-effects meta-analytic) methods to assess the robustness of the results; (2) per-protocol analysis; and (3) IMPACT analysis approach to describe the degree to which each component contributed to the reduction in clinical outcomes.[58] Although the primary analysis will be a direct estimate of the intervention package, we can "deconstruct" the contributions of each component.[59] We will also relate the individual components of the intervention to the change in risk score, and this will allow us to identify the components which are most effective. This information can then be used to develop variations of the interventions, depending on the context.

### Data management, quality, and security

The study will use a mixture of paper and electronic case report forms (CRFs), as appropriate for each community, region, country, and study process. Study personnel will complete either paper CRFs or electronic CRFs using an encrypted, password-protected, portable tablet device or computer securely connected to PHRI's data management platforms via the Internet. With prior consent of the participants, source documentation supporting the trial information reported on the CRFs or electronic CRFs (including verbal narratives of outcome events, medical records or other documents provided by participants, and consent forms, where feasible) will be photographed or recorded by the portable tablet devices during household and clinic visits and securely transmitted to the PHRI data center for event adjudication purposes as well as for central monitoring of the study conduct. Paper CRFs will be collected and reviewed by the National Project Office personnel, with data being submitted to the centralized PHRI system by fax or through secure electronic submission to PHRI's data management platforms.

Data management in HOPE-4 will include the following procedures: (1) National Project Office personnel and community-based teams will undergo training sessions prior to study commencement to ensure consistency in project procedures including data collection and reporting; (2) National Project Offices will have a detailed *Manual of Operations* that will outline each step of the protocol and will be able to communicate with the HOPE-4 Project Office via email to resolve any problems or questions that arise; (3) the PHRI Project Office personnel will review detailed monthly reports on screening, enrollment, patient follow-up, completeness of data collection, and overall study event rates; (4) the centralized PHRI databases will include internal validity and range checks to identify errors or omissions and notify the National Project Offices of any issues; and (5) PHRI personnel will visit National Project Offices (and possibly community-based clinics) for monitoring purposes, as required.

## Health economic evaluation

We hypothesize that this intervention package will improve risk factor control significantly. Although this study is not designed to observe significant reductions in clinical events, we will model the impact of the differences in risk factors to project the differences in clinical events. It is expected that the long-term clinical benefits of this intervention would be at least cost-neutral and potentially cost-saving when compared to current practice. We will collect data that will allow us to determine (1) the cost of the suggested program (ie, intervention package) and
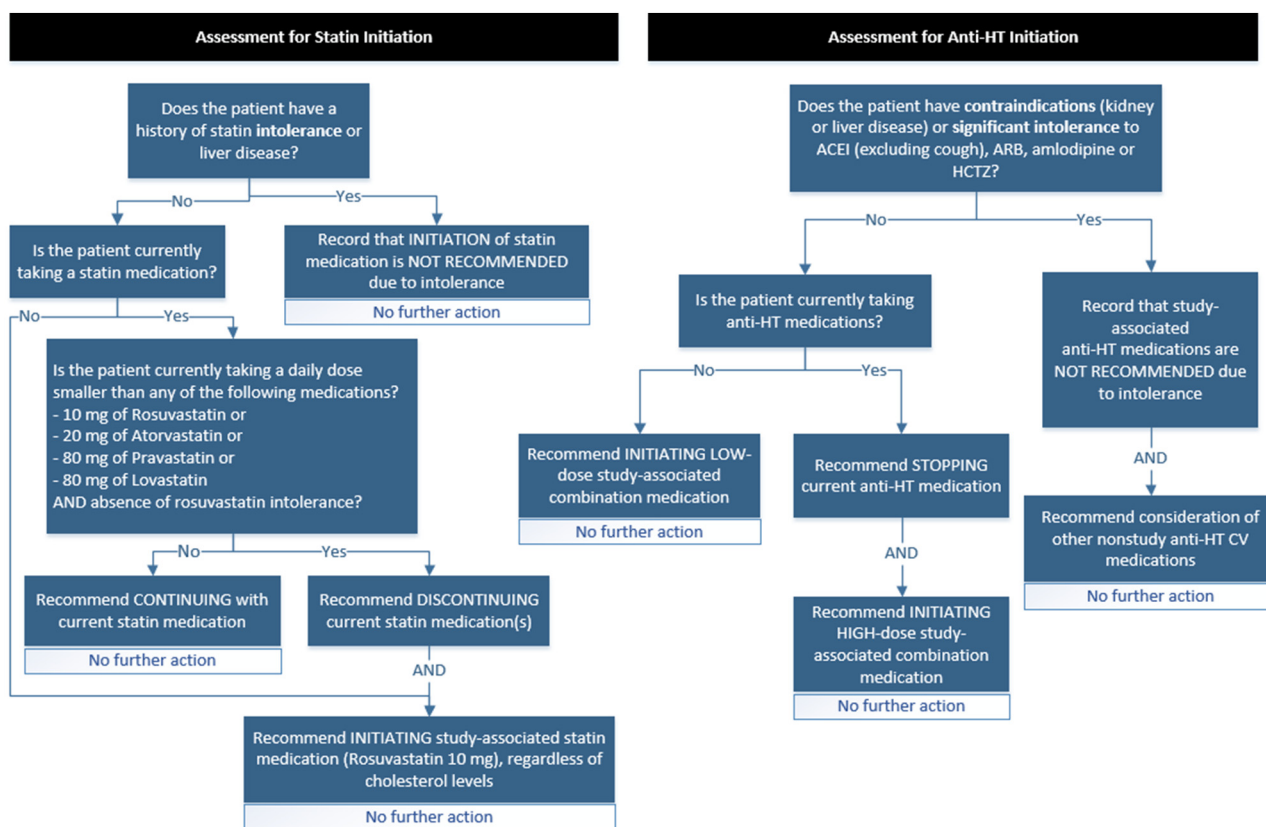
**Figure 3.** Study statin and anti-HT medication algorithms for initiation.

the cost of what is being provided currently for CVD assessment and management in the communities studied (ie, control) and (2) the potential for future cost-savings due to projected reduction in CVD events stemming from the adoption of the program and modeled over a 5-year period based on changes in the FRS.

### Process evaluation

Structured evaluations of new health initiatives are necessary to provide evidence for practice and policy development.[60, 61] Large-scale investigations of a complex intervention—such as HOPE-4—can be complemented and informed by process evaluations conducted in parallel to the main study.[60, 62] In HOPE-4, process evaluations of the role of the NPHWs and treatment supporters, as well as a study of medication adherence, will help inform CVD risk reduction program implementation strategies, post–study completion.

### Ethical considerations

Before study initiation, the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of participating institutions and regulatory authorities approved the HOPE-4 protocol. The IRB/IEC of participating institutions approved the dispensation of study-associated medications to the intervention group alone based on the following: (1) the medications were locally available, (2) the medications were used per accepted indications, and (3) the medications were prescribed by local physicians as per current standards of care. The IRB/IEC also approved that no study-associated medications were to be administered in the control group for the following reasons: (1) the study screening process in the control group already went above usual care by identifying participants with CVD risk (ie, elevated blood pressure), (2) provided them with

locally available management literature, and (3) recommended they seek assessment at a local health care facility.

### Trial status

The HOPE-4 study has randomized 30 communities (1,376 participants) in Colombia and Malaysia (Table VI). All 30 communities will complete 1-year follow-up by the end of 2018. Analysis of completed follow-up data is expected to begin in the first quarter of 2019. At the end of the study, participants will be transitioned to continue current or comparable medication therapy as is available in local communities and will receive guidance from local care providers.

Initial plans for the HOPE-4 study included a CVD phase, with expansion to 190 communities (9,500 participants), 6 years of follow-up, and a difference in cardiovascular events as the primary outcome. Unfortunately, funding limitations prevented expansion to this phase of the HOPE-4 study.

### Discussion

Hypertension is the commonest cause of CVD and the main driver of CVD globally, but its control is poor in almost all countries.[10] The HOPE-4 study involves the integration and implementation of multiple evidence-based strategies to overcome barriers to better hypertension detection, treatment, and control, simultaneous with efforts to modify lipids and other risk factors. If successful, this health system intervention is scalable and sustainable and can be the basis for the development of context-specific approaches in countries at different economic levels. Although the study is taking place in 30 urban and rural communities in Colombia and Malaysia, the rigorous cluster randomized controlled trial

**INTERVENTION**

Complete five scheduled in-person follow-up visits with participants:

   (1) baseline (time-0; includes two visits: participant-NPHW, then participant-physician),
   (2) 1 month,
   (3) 3 months,
   (4) 6 months,
   (5) 12 months.

One additional contact is made over the phone at 10 or 11 months to confirm availability for the final 12 month visit.

**At each intervention visit:**

(a) Take a comprehensive clinical history since last visit (e.g. CV events, symptoms, medications)
(b) Measure BMI and waist and hip measurements at baseline and 12 months
(c) Measure BP
(d) Complete WHO/ISH risk prediction
(e) Apply WHO prevention recommendations (i.e. quitting tobacco use, making healthy food choices, being physically active, reducing alcohol)
(f) Recommend suitable study medications and provide full assessment to study physicians for a prescription decision
(g) Schedule participant-physician appointments when appropriate for a prescription decision

*participants with unusually high BP are asked to immediately seek care at a local clinical centre

**CONTROL**

Complete two scheduled in-person follow-up visits with participants:

   (1) 6 months
   (2) 12 months

Time-0 starts once community is informed of being randomized to control.

Two additional contacts are made over the phone at 3 and 10 or 11 months to confirm availability of the upcoming appointment.

**At each control visit:**

(a) Take a comprehensive clinical history since last visit (e.g. CV events, symptoms, medications)
(b) Perform BMI-relevant measurements (one time)
(c) Measure BP

*participants with unusually high BP are asked to immediately seek care at a local clinical centre

**Figure 4.** NPHW responsibilities in intervention and control groups. *ISH*, International Society of Hypertension; *BMI*, body mass index.

**Table IV**

Minimum detectable differences in mean Framingham risk estimate between intervention and control group at the end of 1-year follow-up (taking into account the effect of clustering and using analysis of covariance)

| | Minimum detectable FRS, % | | |
|---|---|---|---|
| ICC | SD of 15 | SD of 20 | SD of 25 |
| 0.05 | 3.0 | 4.0 | 5.0 |
| 0.07 | 3.4 | 4.9 | 5.6 |

Assuming a sample of size 1200 participants from 2 groups (15 clusters per group, 40 participants per cluster) and a baseline mean (SD) risk of 24.7% (15) with a 2-sided test at 5% label of significance (estimates from the PURE study).

design and associated process evaluations will allow for generalizability of the results to a broader global population.

## Limitations

Given the pragmatic design of this community-based cluster randomized controlled trial, which builds on existing infrastructure within participating countries, blinding is not feasible. Contamination will be minimized, as only those communities randomized to the intervention will have access to the counseling provided by NPHW, simplified

**Table V**

Detectable differences in mean BP and LDL estimate between intervention and control group at the end of 1-year follow-up (taking into account the effect of clustering and using analysis of covariance)

| | Power | |
|---|---|---|
| ICC | Comparing mean BP (mm Hg) | Comparing mean LDL (mmol/L) |
| | 80% | 80% |
| 0.1 | 5.5 | 0.320 |
| 0.05 | 4.3 | 0.243 |
| 0.01 | 2.9 | 0.167 |

Assuming a sample of size 1200 participants from 2 groups (15 clusters per group, 40 participants per cluster) and a baseline mean (SD) SBP of 160 (19) with an ICC = 0.017 and baseline mean (SD) LDL of 3.58 (1.09) with an ICC=0.11 (estimates from PURE study). Two-sided test at 5% label of significance.

management algorithms, and the study-provided medications. In addition, communities have been chosen with adequate geographic separation from each other. Participants in the control group have had CVD risk screening at baseline and have been provided with information about local CV health programs and recommendations. This may reduce the effect of the intervention, as control participants may modify their behavior by seeking medical attention after knowing their BP was not

**Table VI**

Baseline characteristics of participants enrolled in the HOPE-4 study by country, rural/urban stratification, and overall

| | Overall | Location | | Country | |
| --- | --- | --- | --- | --- | --- |
| | | Rural (n = 648) | Urban (n = 728) | Malaysia (n = 616) | Colombia (n = 760) |
| Age, y (mean, SD) | 65.4 (9.4) | 65.4 (9.8) | 65.5 (9) | 62.8 (8) | 67.5 (9.9) |
| Female (%) | 55.8 | 54.7 | 56.8 | 51.1 | 59.7 |
| History of CVD (%) | 5 | 3.3 | 6.4 | 2.5 | 6.9 |
| Current smoker (%) | 8.5 | 10.4 | 6.8 | 13.9 | 4.2 |
| History of DM (%) | 34.7 | 34.1 | 35.3 | 40.0 | 30.3 |
| On statins (%) | 27.7 | 28.3 | 27.1 | 37.0 | 20.2 |
| History of HT (%) | 73.5 | 69.9 | 76.7 | 63.3 | 81.8 |
| HT medication (%) | 66 | 62.5 | 69.2 | 56.9 | 73.4 |
| Systolic BP (mean, SD) | 151.8 (15.5) | 152 (15.4) | 151.7 (15.5) | 153.4 (15.3) | 150.6 (15.5) |
| Diastolic BP (mean, SD) | 85 (11.9) | 84 (12) | 85.8 (11.7) | 86.9 (11.6) | 83.4 (11.9) |
| BMI (mean, SD) | 28 (5.1) | 27.6 (5.3) | 28.2 (5) | 27.9 (5.1) | 28 (5.2) |
| WHR (mean, SD) | 0.93 (0.08) | 0.93 (0.08) | 0.92 (0.08) | 0.91 (0.08) | 0.94 (0.08) |
| Total cholesterol (mean, SD) | 207.1 (46.6) | 208.7 (46.7) | 205.6 (46.5) | 210.4 (48.7) | 204.4 (44.7) |
| HDL cholesterol (mean, SD) | 44.9 (15.6) | 44.3 (15.2) | 45.4 (16) | 45.2 (17.2) | 44.6 (14.1) |
| FRS (mean, SD) | 34.6 (22.2) | 35.3 (22.5) | 33.9 (22) | 35.6 (24.2) | 33.7 (20.4) |
| FRS (median, IQR) | 28.1 (17.7-44.7) | 29 (18-45.9) | 27.5 (17.4-43.9) | 28.7 (16.6-46.8) | 27.9 (18.6-43.4) |

*DM*, Diabetes mellitus; *BMI*, body mass index; *WHR*, waist-hip ratio.

under control at the beginning of the study. This means that the observed differences in risk factors between the active and control groups are likely to be underestimates of the full effects of this intervention strategy.

## Significance

In 2011, the United Nations adopted a global target of a 25% reduction in premature mortality from CVD and other noncommunicable diseases by 2025.[63] The United Nations action plan designated 8 indicators to measure progress, including improvements in (1) BP, (2) tobacco cessation, (3) physical inactivity, (4) sodium intake, (5) alcohol consumption, (6) diabetes and obesity rates, (7) access to drugs and CVD risk prevention counseling, and (8) availability of basic technologies and essential medicines.[64] Similar elements are included in the Sustainable Development Goals. The HOPE-4 program is designed to address all 8 components with a focus on BP and lipids. This low-cost strategy using inexpensive generic medications, coupled with low-cost NPHWs supported by novel mhealth systems to reach and serve at-risk populations, can tackle one of the largest contributors to the global disease burden and potentially save millions of lives each year. Furthermore, this strategy is applicable to both HICs and LMICs so that, if successful, it can have a significant global impact and be incorporated into the health systems of many different countries. The HOPE-4 program has similarities to the approach taken in a variety of other successful health system strategies dealing with other conditions (eg, HIV, TB, malaria, immunizations) and even to some extent the management of heart failure in HIC. Therefore, given the simplicity and safety of the approach, the HOPE-4 program has the potential to make a significant impact on the burden of CVD.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.06.004.

## References

1. Iburg KM. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet 2017;390:1260-344.
2. Doku D. *Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: A systematic analysis for the Global Burden of Disease Study 2016. 2017.*
3. World Health Organization. *Global Health Observatory (GHO) data: NCD mortality and morbidity. 2015.*
4. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the Interheart study): case-control study. Lancet 2004;364:937-52.
5. Smith Jr SC, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update endorsed by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol 2006;47: 2130-9.
6. Yusuf S, Pais P, Sigamani A, et al. Comparison of risk factor reduction and tolerability of a full-dose polypill (with potassium) versus low-dose polypill (polycap) in individuals at high risk of cardiovascular diseases: the Second Indian Polycap Study (TIPS-2) Investigators. Circ Cardiovasc Qual Outcomes 2012;5:463-71.
7. Khatib R, Schwalm JD, Yusuf S, et al. Patient and healthcare provider barriers to hypertension awareness, treatment and follow up: a systematic review and meta-analysis of qualitative and quantitative studies. PLoS One 2014;9, e84238.
8. Risso-Gill I, Balabanova D, Majid F, et al. Understanding the modifiable health systems barriers to hypertension management in Malaysia: a multi-method health systems appraisal approach. BMC Health Serv Res 2015;15:254-69.
9. Legido-Quigley H, Lopez PAC, Balabanova D, et al. Patients' knowledge, attitudes, behaviour and health care experiences on the prevention, detection, management and control of hypertension in colombia: a qualitative study. PLoS One 2015;10, e0122112.
10. Chow CK, Teo KK, Rangarajan S, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA 2013;310:959-68.
11. Kearney PM, Whelton M, Reynolds K, et al. Worldwide prevalence of hypertension: a systematic review. J Hypertens 2004;22:11-9.
12. Lopez AD, Mathers CD, Ezzati M, et al. *Global burden of disease and risk factors. 2006.*
13. Statistics Canada. *Selected leading causes of death. 2005. [accessed March 28, 2007].*
14. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE study): a prospective epidemiological survey. Lancet 2011;378: 1231-43.
15. Khatib R, McKee M, Shannon H, et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the pure study data. Lancet 2015;387:61-9.
16. Maimaris W, Paty J, Perel P, et al. The influence of health systems on hypertension awareness, treatment, and control: a systematic literature review. PLoS Med 2013;10(7), e1001490. https://doi.org/10.1371/journal.pmed.1001490.
17. Nieuwlaat R, Schwalm JD, Khatib R, et al. Why are we failing to implement effective therapies in cardiovascular disease? Eur Heart J 2013;34:1262-9.
18. Neupane D, McLachlan CS, Mishra SR, et al. Effectiveness of a lifestyle intervention led by female community health volunteers versus usual care in blood pressure reduction (COBIN): an open-label, cluster-randomised trial. Lancet Glob Health 2018;6: e66-73.
19. Abegunde DO, Shengelia B, Luyten A, et al. Can non-physician health-care workers assess and manage cardiovascular risk in primary care? Bull World Health Organ 2007;85:432-40.
20. Ahmed T, Jakaria SM. Community-based skilled birth attendants in bangladesh: attending deliveries at home. Reprod Health Matters 2009;17:45-50.
21. Gandhi S, Chen S, Hong L, et al. Effect of mobile health interventions on the secondary prevention of cardiovascular disease: systematic review and meta-analysis. Can J Cardiol 2017;33:219-31.

22. Lamelas PM, Yusuf S, Schwalm J. Effective approaches to address the global cardiovascular disease burden. Curr Opin Cardiol 2017;32:557-66.
23. World Health Organization. *WHO CVD-risk management package for low- and medium-resource settings. Geneva: World Health Organization. 2002.*
24. World Health Organization. *Task shifting to tackle health worker shortages. 2007:1-9.*
25. Campbell NR, Poirier L, Tremblay G, et al. Canadian Hypertension Education Program: the science supporting new 2011 CHEP recommendations with an emphasis on health advocacy and knowledge translation. Can J Cardiol 2011;27:407-14.
26. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2010;56:e50-e103.
27. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87.
28. López-Jaramillo P, Sánchez RA, Díaz M, et al. Latin American consensus on hypertension in patients with type 2 diabetes and metabolic syndrome. Rev Med 2013;21:113-35.
29. Garg AX, Adhikari NK, McDonald H, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005;293:1223-38.
30. Kawamoto K, Houlihan CA, Balas EA, et al. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ 2005;330:765-73.
31. Praveen D, Patel A, McMahon S, et al. A multifaceted strategy using mobile technology to assist rural primary healthcare doctors and frontline health workers in cardiovascular disease risk management: protocol for the Smarthealth India cluster randomised controlled trial. Implement Sci 2013;8:137-45.
32. Van Camp YP, Van Rompaey B, Elseviers MM. Nurse-led interventions to enhance adherence to chronic medication: systematic review and meta-analysis of randomised controlled trials. Eur J Clin Pharmacol 2013;69:761-70.
33. Vedanthan R, Kamano JH, Naanyu V, et al. Optimizing linkage and retention to hypertension care in rural Kenya (LARK hypertension study): study protocol for a randomized controlled trial. Trials 2014;15:143-54.
34. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206-52.
35. Lonn EM, Bosch J, López-Jaramillo P, et al. Blood-pressure lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2009-20.
36. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021-31.
37. Yusuf S, Lonn E, Pais P, et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. N Engl J Med 2016;374:2032-43.
38. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149-58.
39. Khatib R. Barriers to the management of cardiovascular disease: a focus on availability and affordability of medications in 17 countries. Clinical Epidemiology and Biostatistics, Health Research Methodology Program; 2014.. [PhD].
40. Nachega JB, Chaisson RE, Goliath R, et al. Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy. AIDS 2010;24:1273-80.
41. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for imrovement. J Am Med Assoc 1999;282(15):1458-65. https://doi.org/10.1001/jama.282.15.1458.
42. World Health Organization. WHO: everybody's business: strengthnening heath systems to improve health outcomes. WHO's Framework for Action; 2007.
43. Schwalm Jon-David, McKee Martin, Huffman Mark D, et al. Resource effective strategies to prevent and treat cardiovascular disease. Circulation 2016;133:742-55.
44. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Ann Intern Med 2010;8:18-27.
45. Khan M, Lamelas P, Musa H, et al. Development, testing, and implementation of a training curriculum for nonphysician health workers to reduce cardiovascular disease. Glob Heart 2018.
46. Schwalm JD, AD, Zarate M, et al. *HOPE-4 technical paper on the mhealth tablet (temporary unpublished title). 2018. [unknown at the moment;Not in press yet].*
47. Package of essential ncd interventions for primary health care: cancer, diabetes, heart disease and stroke, chronic respiratory disease. 2010.
48. World Health Organization. *The WHO stepwise approach to noncommunicable disease risk factor surveillance. 2017. [3-5-5].*
49. Artigao-Rodenas LM, Carbayo-Herencia JA, Divison-Garrote JA, et al. Framingham risk score for prediction of cardiovascular diseases: a population-based study from southern europe. PLoS One 2013;8, e73529.
50. Chia YC, Gray SY, Ching SM, et al. Validation of the Framingham general cardiovascular risk score in a multiethnic asian population: a retrospective cohort study. BMJ Open 2015;5, e007324.
51. Framingham Heart Study. Cardiovascular disease (10-year risk). Framingham Heart Study: a project of National Heart, Lung, and Blood Institute and Boston University; 2018.
52. Teo K, Chow CK, Vaz M, et al. The prospective urban rural epidemiology (pure) study: Examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. Am Heart J 2009;158:1-7.e1.
53. Marjan WA, Khatib R, McKee M, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: an analysis of the pure study data. Lancet Public Health 2017;2:e411-9.
54. Campbell MK, Piaggio G, Elbourne DR, et al. CONSORT 2010 statement: extension to cluster randomised trials. BMJ 2012;345, e5661.
55. Schafer JL *Analysis of incomplete multivariate data. Chapman & Hall/CRC: Boca Raton, FL. 1997.*
56. Ma J, Thabane L, Kaczorowski J, et al. Comparison of bayesian and classical methods in the analysis of cluster randomized controlled trials with a binary outcome: the Community Hypertension Assessment Trial (CHAT). BMC Med Res Methodol 2009;9:37-46.
57. Hardin JW. *Generalized estimating equations. Chapman & Hall/CRC: Boca Raton, FL. 2003.*
58. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. Deaths from coronary disease, 1980-2000. N Engl J Med 2007;356:2388-98.
59. Hardin JW, Hilbe JM. *Generalized estimating equations. Chapman & Hall/CRC: New York, NY. 2002.*
60. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419-25.
61. Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002;360:2-3.
62. Law MR, Wald NJ, Morris JK, et al. Value of low dose combination treatment with blood pressure lowering drugs: Analysis of 354 randomised trials. BMJ 2003;326:1427-35.
63. Mamudu HM, Yang JS, Novotny TE. Un resolution on the prevention and control of non-communicable diseases: AN opportunity for global action. Glob Public Health 2011;6:347-53.
64. World Health Organization. *2008-2013 action plan for the global strategy for the prevention and control of noncommunicable diseases. 2009.*