Hypertension Control Program in Argentina
(HCPIA)

PROTOCOL

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1. Overview

Hypertension is the leading cause of cardiovascular diseases (CVD) and premature death in the world.\(^1\) It was estimated that, globally, 26.4% of the adult population in 2000 had hypertension and 29.2% were projected to have hypertension by 2025.\(^2\) The highest estimated prevalence of hypertension was in Latin America: 40.7% in men and 34.8% in women. Although the efficacy and effectiveness of lifestyle modifications and antihypertensive pharmaceutical treatment for the prevention of hypertension and concomitant CVD and premature death have been demonstrated in randomized controlled trials,\(^3,4\) this scientific knowledge has not been fully applied in the general population, especially in low and middle income countries.\(^5\) In these countries, the prevalence of hypertension continues to be high and is increasing while the proportions of hypertensive patients who are aware, treated, and controlled are unacceptably low.\(^2,6\) Many barriers at the health care system, health care provider, and patient levels have been identified that impede hypertension control in populations.\(^7\) There is an urgent need to identify innovative strategies to overcome these barriers and to deliver effective interventions for hypertension control in populations in low and middle income countries.

The overall objective of this study is to test whether a comprehensive intervention program within a national public primary care system will improve hypertension control among uninsured hypertensive patients and their families in Argentina. The comprehensive intervention program will target the primary care system through health care provider education, a home-based intervention among patients and their families (home delivery of antihypertensive medication, home blood pressure [BP] monitoring, health education for medication adherence and lifestyle modification) conducted by community health workers (CHW), and a mobile health intervention. In addition, we will disseminate the study findings and scale-up the proven effective intervention program to the entire national public primary care network in Argentina. Specifically, we will conduct a cluster randomized trial among 18 public primary care clinics within the national network in Argentina: 9 clinics will be assigned to a comprehensive intervention program and 9 clinics to usual care.

The specific aims of this cluster randomized trial are:

1. To test whether a comprehensive intervention program will lower systolic and diastolic BP among hypertensive patients over an 18-month period, compared to usual care;
2. To evaluate whether a comprehensive intervention program will improve hypertension control among hypertensive patients over an 18-month period, compared to usual care; and
3. To estimate the cost-effectiveness of this comprehensive intervention program compared to usual care.

We will recruit 1,890 study participants from 18 public primary care clinics within a national network. Nine clinics with approximately 945 participants will be randomly assigned to the intervention group and 9 clinics with similar participants to the control group. Patients with hypertension from the participating clinics and their spouses, as well as adult family members with hypertension, will be enrolled. The comprehensive intervention will last for 18 months. BP and other indicators will be measured at baseline and months 6, 12, and 18 during follow-up using standard methods. The primary outcome is a net change in systolic (SBP) and diastolic BP (DBP) from baseline to month 18 between the
intervention and control groups among hypertensive study participants. The secondary outcomes are the proportion of hypertensive patients with adequate BP control (BP<140/90 mmHg), net BP changes in normotensive participants, and cost-effectiveness. The proposed trial is designed to provide 80% statistical power to detect a ≥3.74 mm Hg mmHg reduction in SBP at a significance level of 0.05 using a 2-tailed test. In addition, we have 80% power to detect a 41% increase in hypertension control (from 42.9% to 60.7%). An 85% follow-up rate was assumed and the cluster design was taken into consideration in the power calculation.

This is a joint project of the Tulane University School of Public Health and Tropical Medicine in the US and the Institute for Clinical Effectiveness and Health Policy in Argentina. We will partner with the national public primary care network (the Remediar+Redes program) of Argentina in conducting this implementation research project. All interventions, including health care provider education, lifestyle modification, home BP-monitoring, and mobile health interventions, have been documented to be effective on hypertension control in previous clinical trials conducted in the US and other developed countries. The innovation of this implementation study includes: (1). A comprehensive intervention program including many previously proven interventions targeting hypertensive patients and their families; (2). Utilization of CHW to deliver the interventions at patients’ homes; (3). Emphasis on the elimination of health disparity through hypertension control in uninsured populations; (4). Immediate impact in the real world by data dissemination and scale-up of the intervention program to the entire national public primary care network; and (5). Strong support from healthcare decision-makers. This study will generate urgently needed data on effective, practical, and sustainable intervention programs aimed at controlling hypertension and concomitant CVD. The results from this study may be directly used in other primary care settings and healthcare systems in low and middle income countries for the prevention and control of hypertension.

2. Background and Significance

2.A. Hypertension as a Major Public Health Challenge

Hypertension is a global public-health challenge because of its high prevalence and the concomitant increase in risk of CVD.\(^1\) It was estimated that 26.4% of the world adult population in 2000 had hypertension and 29.2% were projected to have hypertension by 2025.\(^2\) The highest estimated prevalence of hypertension was in Latin America: 40.7% in men and 34.8% in women. Hypertension is a leading global risk factor for CVD and premature death.\(^1,8\) It was estimated that 7.6 million premature deaths (about 13.5% of the global total) were attributed to high BP worldwide.\(^8\) In addition, about 54% of stroke and 47% of coronary heart disease (CHD) worldwide were attributable to high BP.\(^5\)

2.B. Prevalence, Awareness, Treatment, and Control of Hypertension in Argentina

The 2009 Argentina National Risk Factor Survey conducted by the Ministry of Health indicated that 34.8% of adults (31.6% of men and 36.8% of women) have self-reported hypertension.\(^9\) Of them, 54.2% received antihypertensive drug treatment. The Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study included a sample of 1,482 participants from Buenos Aires, Argentina.\(^10\) The prevalence of hypertension was 29.0%, the highest among the 7 Latin American cities selected;
35.9% of hypertensives were unaware of their status and only 18.0% were treated and controlled, the lowest among the 7 cities included.\textsuperscript{10}

Age-standardized CVD mortality was 206.4/100,000 persons, representing 34.2% of all deaths in Argentina.\textsuperscript{11} We have shown that >600,000 disability adjusted life years (DALYs) were lost in 2005 in Argentina due to CHD and stroke.\textsuperscript{12} Hypertension explained 37.0% of all CHD and stroke events and 36.6% of all DALYs lost in 2005.\textsuperscript{13} Hypertension is the most important risk factor for CHD and stroke in Latin America.\textsuperscript{14,15}

2.C. Lifestyle Modification for the Prevention and Treatment of Hypertension

Several lifestyle interventions have been recommended for the prevention and treatment of hypertension.\textsuperscript{3,4}

- **Weight loss**: Prospective studies consistently reported that overweight/obesity increased the risk of hypertension\textsuperscript{16-18}, while randomized controlled trials demonstrated weight loss reduced BP.\textsuperscript{19,20}

- **Decrease sodium intake**: Evidence from observational studies,\textsuperscript{21,22} laboratory animal studies,\textsuperscript{23,24} and clinical trials\textsuperscript{25,26} demonstrated a causal relationship between dietary sodium intake and elevated BP.

- **Increase physical activity**: Prospective studies identified an inverse association between physical activity and BP.\textsuperscript{17,27} Clinical trials documented exercise lowering BP in hypertensive and normotensive individuals.\textsuperscript{28,29}

- **Reduce excessive alcohol intake**: Prospective studies and randomized trials documented a dose-response relationship between mean alcohol reduction and mean BP reduction.\textsuperscript{30}

- **Increase potassium intake**: Numerous randomized controlled trials demonstrated that potassium supplementation lowers BP in hypertensive and normotensive individuals.\textsuperscript{31}

- **Consume a healthy diet**: The vegetarian diet was associated with lower BP levels in observational studies.\textsuperscript{32,33} A diet rich in fruits and vegetables and in low-fat dairy products with reduced saturated and total fat (DASH diet) significantly reduced BP in the Dietary Approaches to Stop Hypertension (DASH) trial.\textsuperscript{34} A combination of the DASH diet and sodium reduction further reduced BP in the DASH-Sodium Trial.\textsuperscript{35}

The current challenge is to integrate lifestyle modifications into comprehensive intervention programs for the prevention and control of hypertension in populations.

2.D. Antihypertensive Pharmaceutical Treatment

Randomized controlled trials have demonstrated that treatment with any commonly-used antihypertensive regimen reduces the risk of major CVD events and total mortality.\textsuperscript{36-43} For example, antihypertensive treatment has been associated with reductions in stroke incidence averaging 35% to 40%; myocardial infarction, 20% to 25%; and heart failure (HF) >50%.\textsuperscript{43} Antihypertensive treatment also slows the progression of CKD in randomized trials.\textsuperscript{44-46} Although the efficacy and effectiveness of antihypertensive treatment on major vascular events and total mortality have been demonstrated in randomized trials, this beneficial effect has not been maximized in general populations.\textsuperscript{7} The proportion of individuals with
hypertension who were treated and controlled is low, especially in low and middle income countries (LMIC).6

2.E. Barriers to Hypertension Control

2.E.1. Health care system

Lack of access to health care, medication cost, and poor insurance coverage are major system level barriers to hypertension prevention and control.7 Additional barriers include multiple competing demands on physician time and lack of reimbursement for preventive counseling.47,48

2.E.2. Health care providers

Provider-level barriers include lack of adherence to guidelines, willingness to accept elevated BP, and failure to prioritize BP among multiple chronic medical issues.47 Surveys have identified many reasons for failure to adhere to published guidelines including uncertainty that clinical BP levels are representative of patients’ usual BP, hypertension not being a priority for the visit, and patient non-adherence with medications already prescribed.49 In addition, studies suggest that physicians significantly overestimate their adherence to treatment guidelines and hypertension control rates among their patients.50,51

2.E.3. Patients

Patient-level barriers to BP control are primarily related to therapy adherence, and include low perceived risks of high BP, low health literacy, lack of motivation, out-of-pocket medication costs, and adverse side effects.47,52,53 Adherence to antihypertensive medications is difficult because they are costly, prone to side effects, and no benefit is immediately observed.54 A cohort study of hypertensive patients newly prescribed antihypertensive medications found that 43.3% discontinued the medication within the first year, and those who did so were more likely to report side effects.55

2.F. Interventions to Improve Hypertension Prevention and Control

2.F.1. Physician education

Interactive physician educational programs have resulted in moderate to large improvements in professional practice.56-58 In addition, printed educational materials appear to have a small beneficial effect on professional practice.59 Physician education interventions specific to BP control have resulted in a median reduction in SBP of 3.3 mmHg (from 11 trials) and DBP of 0.6 mmHg (from 16 trials).60 Continuing medical education is part of the certification/re-certification process in specialty medical societies in Argentina and can be a motivational tool to encourage physician education on hypertension guidelines.

2.F.2. Family-base education

BP lowering trials with a patient education component in a multi-factorial intervention have been successful in lowering BP and controlling hypertension.61-65 A systematic review of hypertension management interventions found a median reduction of 8.1 mmHg for SBP and 3.8 mmHg for DBP, as well as median 19.2% and 17.0% increases in SBP and DBP control, respectively, in studies with a patient education component.66 Patient reminding strategies (encouraging patients to keep appointments or adhere to treatment) have been effective for improving BP control in hypertension.50,66-69 In comparison to
individual education, family-based education has the added advantages of built-in social support and accountability, and targets shared lifestyle changes, such as food preparation and leisure time activities. Social support has a positive impact on many chronic disease outcomes, including hypertension. In addition, spouses of patients with hypertension are more likely to have high BP than spouses of normotensives, so targeting interventions at the family could also lower BP of high risk individuals who are not the primary patient.

2.F.3. Home blood pressure monitoring

BP monitoring outside of a clinical setting is an effective tool in the management of hypertension. Compared to measurements in a physician’s office or clinic, home BP monitoring minimizes the “white coat” effect and allows for frequent and multiple readings. Since some physicians are hesitant to treat hypertension based on clinic measurements alone, home BP monitoring can provide additional BP measurements leading to better treatment decisions. Home BP monitoring using electronic cuffs has been shown to be more effective in reducing BP and reaching target BP goals than BP monitoring in a clinical setting alone. In addition, home BP measurements are better predictors of CVD incidence and mortality, and target organ damage than clinical measurements.

2.F.4. Community health workers

CHW can increase the capacity of an already overburdened health care system by using health care resources effectively and increasing the quality of care. The addition of CHW to the clinical team is an example of organizational or team change, which addresses systems-level barriers to hypertension prevention and control by simplifying the physician’s tasks and transferring some responsibility for patient care to another team member. Team change strategies have resulted in median reductions in SBP of 9.7 mmHg in 20 studies and in DBP of 4.2 mmHg in 24 studies. In addition, CHW may remove barriers to BP control and medication adherence due to cultural, educational, and language differences between community members and the health care system. A systematic review of randomized trials using CHW to implement BP control programs found significant improvement in 7 of 8 studies, primarily in poor, urban, minority communities. Trials in low and middle income countries have also seen reductions in BP using CHW-delivered programs, including trials in Pakistan and Ghana.

2.F.5. Mobile health interventions

Cell phones and text messaging are already a part of daily life and have great potential for supporting behavior change. Mobile health (mHealth) refers to using mobile telecommunication and multimedia technologies for health-related purposes. For example, in the txt2stop trial of mobile phone text messages to support smoking cessation, biochemically verified smoking cessation at 6 months was 10.7% in the intervention group vs. 4.9% in the control group (p<0.0001). A recent review of text messaging or email interventions identified 16 randomized trials of which 10 reported significant improvement in outcomes and 6 reported differences suggesting positive trends. mHealth is emerging as a useful tool to address several health system constraints in low and middle income countries. Telephone disease management strategies have been successful in improving health outcomes in Latin America, and in Argentina specifically. According to the World Bank, between 2006-2009, Argentine cellular phone subscriptions increased from 81 to 129 per 100 people. In a recent systematic review, we found that
mHealth is cost-effective and has positive impacts on health care processes, clinical outcomes and quality of life among 9 randomized trials in LMIC.

2.G. Rationale for a Comprehensive Intervention for Hypertension Control

Recent randomized trials have shown that a comprehensive intervention strategy is more effective in hypertension control than individual components. In the Hypertension Improvement Project (HIP), a 2 x 2 randomized trial of physician and patient interventions, there was a significant interaction between physician and patient interventions, and the greatest improvement was seen in the group with both interventions. Similarly, reviews examining the translation of guidelines into practice have demonstrated that isolated strategies are largely ineffective, whereas integration of multiple intervention strategies (even those that are ineffective in isolation) in the appropriate context and setting results in improved outcomes. Given the complex nature of barriers to hypertension prevention and control, a comprehensive, sustainable approach to interventions focusing on multiple domains is not only advantageous but necessary.

2.H. Cost-effectiveness of Hypertension Intervention

Antihypertensive treatment reduces the risk of CVD and total mortality Several studies showed that the cost-effectiveness ratio of antihypertensive treatment is similar or better than lipid-lowering or hypoglycemic therapies. The cost-effectiveness of antihypertensive treatment depends on initial untreated BP levels, absolute risk of CVD, cost of medications, and more importantly, the ability to achieve and maintain target levels of BP over time. However, data on the cost-effectiveness of intervention programs aimed at improving hypertension prevention and control are still scarce.

2.I. Public Health Impact

Hypertension is a leading public health challenge in the world due to its high prevalence and consequent risk of CVD and premature deaths. Although the efficacy and effectiveness of lifestyle modifications and antihypertensive drug treatment on the prevention of hypertension and consequent CVD risk have been demonstrated in randomized controlled trials, this scientific knowledge has not been fully applied in the general population, especially in low and middle income countries (LMIC). There is an urgent need to implement innovative strategies for improving the prevention and control of hypertension in LMIC populations. The proposed study will test whether a comprehensive intervention program within a public primary care system will improve hypertension control among uninsured hypertensive patients and their families in Argentina. All interventions, including health care provider education, home delivery of antihypertensive medication, lifestyle modification, home BP-monitoring, and mobile health interventions have been documented to be effective for hypertension control in previous clinical trials conducted in the US and other developed populations. This study will generate urgently needed data on effective, practical, and sustainable intervention programs aimed at control of hypertension and concomitant CVD. The results from this trial may be directly used by other primary care settings and healthcare systems in LMICs for the prevention and control of hypertension.

2.J. Innovation

This trial is designed with an implementation focus rather than to test the effectiveness of a new intervention according to the RFA. The unique aspects of study are:
- **Comprehensive intervention program**: We take advantage of intervention strategies previously proven effective and develop a comprehensive intervention program, which will be tested and implemented in a national public primary care network in Argentina.

- **Targeting a high risk group and home-based intervention**: Family members of hypertensive patients are at high risk due to shared environmental and genetic factors. Family-based interventions are especially effective for lifestyle change and provide social support for adherence to intervention programs.

- **Use of mobile health intervention**: Text messages/emails will be used for supporting behavior change.

- **Low cost implementation**: Our study will employ community health workers to implement the intervention program, which is a practical and sustainable approach for large-scale and long-term interventions.

- **Elimination of health disparity**: Our study will target the uninsured population and will, thereby, reduce health disparities in hypertension prevention and control.

- **Dissemination and scale-up**: The results from the proposed study will have an immediate impact in the real world through the dissemination and scale-up of the intervention program to the entire national public primary care network in Argentina. In addition, the study findings/intervention may be directly used by other primary care settings and healthcare systems in LMIC for the prevention and control of hypertension.

### 3. Research Design and Organization

#### 3.A. Overview of the Trial Design

We will test whether a comprehensive intervention program compared to usual care within a public primary care network will improve hypertension prevention and control among uninsured hypertensive patients and their families in Argentina. We will utilize a cluster randomized design and assign 18 primary care clinics (centers for primary health care, CPHC) within a national public primary care network (Programa Remediar+Redes) to the intervention or control groups *(Figure 1)*. The trial will recruit 1,890 study participants from 18 primary care clinics within the Remediar+Redes program: 9 clinics with approximately 945 participants in the intervention group and 9 clinics with similar participants in the control group. Patients with hypertension from the participating primary care clinics and their adult family members will be enrolled. The comprehensive intervention program, including health care provider education, home-based intervention among patients and their families (home delivery of antihypertensive medication, home BP monitoring,
health education for medication adherence and lifestyle modification) conducted by CHWs, and a mobile health intervention, will last for 18 months. If proven effective, we will disseminate the study findings and scale-up the program to the entire national public primary care network in Argentina.

3.B. Study Organization and Communication

The study organization structure is illustrated in Figure 2.

3.B.1. Study steering committee

The proposed trial will be overseen by a Study Steering Committee, which will be chaired by the PI and consists of the co-PI from the Field Coordinating Center (FCC) and investigators from each clinic. A NHLBI Project Scientist and a representative from the Remediar+Redes program will also be invited to attend the Study Steering Committee meetings. The committee will oversee the study design and conduct, data analysis, and reporting of study findings. The Study Steering Committee will also serve as the Data Safety Monitoring Committee for the study. In this capacity, they will monitor patient safety issues as the trial progresses.

The Steering Committee will meet annually in-person and monthly by conference call to discuss and make decisions on important study-related scientific and management issues. Important information, such as recruitment yields, data completion and quality, and adherence to the protocol, will be sent to committee members and core staff by e-mail monthly. In addition, investigators will use e-mail communication frequently.

3.B.2. Study and data coordinating center

The Study and Data Coordinating Center (SDCC) will be located at Tulane University School of Public Health and Tropical Medicine. The SDCC will work closely with the Study Steering Committee, Field Coordinating Center, and the NHLBI Project Scientist to provide scientific and administrative support for the trial. The SDCC will also be responsible for all data coordinating responsibilities, including development of a study website for study-wide communication and a database and data entry system, conduct randomization, data quality control, preparation of reports to the Steering Committee and the Data and Safety Monitoring Committee, and data analysis. Regularly scheduled meetings will take place to facilitate communication between investigators and SDCC staff.

3.B.3. Field coordinating center

The Field Coordinating Center (FCC), located at IECS, will work with each clinic on patient recruitment, conduct of the intervention, follow-up of study participants, data collection, and quality control. To facilitate communication among investigators, FCC staff, and clinical research staff, regularly scheduled meetings will take place.

3.B.4. Communications

The Steering Committee will meet face-to-face once a year and participate in monthly conference calls to discuss and make decisions on important study-related scientific and management issues. In
addition, investigators will use e-mail communication frequently. Important information, such as recruitment yields, data completion, and adherence to the protocol will be sent to committee members and core staff by fax or e-mail monthly. Within each clinic, weekly investigator and staff meetings will be held to discuss potential problems related to patient recruitment, intervention, adherence, follow-up, data collection, quality control or other issues.

4. Study Population

4.A. Argentine Health Care System

According to 2010 census data, Argentina has 40 million residents and 90% of the population is urban. Its health care system includes three sectors: the public sector, financed through taxes; the social security sector, financed through obligatory insurance schemes; and the private sector, financed through voluntary insurance schemes. About 35% of the Argentine population, mostly the poorest, have no insurance and rely solely on the public health sector of each province or district. Health care for the uninsured in Argentina is provided by an overloaded public primary care network, consisting of primary care clinics (centers for primary health care, CPHCs) and hospitals.

4.B. Programa Remediar+Redes

Argentina experienced a severe socioeconomic crisis at the end of 2001 that caused a 42% drop in access to medications among the population, especially in the poor who no longer had access to free medications. In response to this crisis, the government created the Programa Remediar+Redes (http://www.remediar.gov.ar/), under the authority of the National Ministry of Health. This program provides free ambulatory drugs to vulnerable people without health insurance who attend public primary care clinics. Over the past decade, the program evolved into the main public primary health care network in the country involving almost all the provinces and municipalities of Argentina and covering almost 7,000 public primary care clinics around the country (>90% of all public clinics). Apart from the provision of free medicine, the implementation of the network shifted the number of ambulatory visits from the hospitals to the CPHCs (35% to 53% over the last decade), where preventive and primary care services are more appropriately delivered. According to recent national data, 65% of free medicine used in primary care centers was supplied by the Remediar+Redes program. Currently, the program’s main missions are: 1. to strengthen health networks through provincial projects and local projects aimed at promoting community participation; 2. to provide essential drugs to almost 7,000 clinics for primary health care; and 3. to train and retrain health care providers in primary health care.

Three antihypertensive drugs are provided to hypertensive patients free of charge under public coverage as essential medications: hydrochlorothiazide, enalapril, and atenolol. Although access and coverage of antihypertensive treatment has expanded for uninsured people in Argentina, the health disparity is still a serious problem. A recent study that analyzed prescriptions to hypertensive patients seen at over 6,000 CPHCs reported that only 57% of uninsured hypertensive patients covered by the Remediar+Redes program were treated. In those treated, almost 75% of patients received medication for ≤4 months/year and only 11.8% received it for ≥9 months/year. Despite the availability and provision of free antihypertensive drugs, the proportions of hypertensive patients who were treated and controlled were low in CPHCs due to access issues and non-adherence among healthcare providers and patients.
4.C. Centers for Primary Health Care Eligibility Criteria

There are 6,956 CPHCs affiliated with the Remediar+Redes program. We will work with the coordination unit of the Remediar+Redes program to select 18 CPHCs for the proposed study. We will review documentation related to the number of outpatient visits and contact the directors of potential CPHCs to inquire about their interest and willingness to participate. Other selection criteria will include prior participation in research studies or activities and their geographical location, in order to ensure a balanced representation of the major sub-regions of the country. The research team will invite the selected CPHCs to participate in the trial after an audit to determine final eligibility.

**Inclusion criteria for CPHCs:**
- The clinic is affiliated with the Remediar+Redes program.
- The clinic is located in urban poor areas according to the 2010 census data.
- The clinic has ≥1000 outpatient visits each month, so that sufficient participants can be recruited.
- The minimum distance between the selected CPHCs will be 10 kilometers to minimize the risk for contamination of the intervention.
- Physician visits and essential medications are free of charge to patients under all circumstances.
- The clinic has a high number of prescriptions for antihypertensive medications.
- The clinic employs community health workers.
- The clinic has general practitioners and nurses.
- The clinic has a history of good performance in the Remediar+Redes program.
- The clinic performs blood draws on patients when appropriate.

4.D. Study Participant Eligibility Criteria

In this implementation study, we aim to recruit participants from “real world” clinical settings with minimum eligibility criteria.

**Inclusion criteria for participants:**
- Patients aged ≥21 years who received primary care from the participating CPHCs and have hypertension (use of antihypertensive medications or SBP ≥140 mmHg and/or DBP ≥90 mmHg on at least 2 separate visits) and their spouses (with or without hypertension) will be included. In addition, any adult family members (age ≥21 years) with hypertension living in the same household will also be included.
- Hypertension patients and their spouses must be available for the first baseline nurse home visit.
- The family’s homes must be located within 10 kilometers from the clinic.

**Exclusion criteria for participants:**
- Hypertension patients who do not have a spouse or another adult with hypertension in the household.
- Plans to move from the neighborhood in the next two years
- Pregnant women or women who are planning to become pregnant in the next two years
• Persons who are bed-bound
• Persons who cannot give informed consent

4.E. Recruitment

Each CPHC will recruit 45-50 hypertensive patients and their spouses, as well as adult family members with hypertension (45-50 households), for the proposed study over the recruitment period of 18 months. We anticipate recruiting approximately 105 individuals from each CPHC for the proposed study. Of them, at least 73 (48 + 48×34% + 9) participants have hypertension. Given each CPHC has ≥1,000 outpatient visits each month, and over 50% of patients have hypertension based on our previous experience, there is a large pool of potential participants for the proposed study in each eligible CPHC. Refusal rates will be recorded at each CPHC and reported to the coordinating center.

The research nurses will review the clinic appointment schedules daily and identify patients with hypertension. They will meet with patients prior to or after their physician visit for prescreening to assess their eligibility. Age and gender quotas will be used at each clinic for recruitment. Eligible patients will be invited along with their family to participate in the study, and the research nurse will make an appointment for subsequent baseline nurse home visits at a time when all family members can be present.

5. Randomization

The 18 selected centers for primary health care (CPHC) fulfilling the inclusion criteria matched by geographic regions are randomized to either the intervention or the control group: 9 CPHCs to intervention and 9 to control group. The randomization is stratified by geographic regions: Buenos Aires (6 CPHCs), Misiones (4 CPHCs), Tucuman (4 CPHCs), Corrientes (2 CPHCs), and Entre Ríos (2 CPHCs). The randomization is conducted at the SDCC at Tulane University in the US.

6. Intervention

We will test a comprehensive intervention program addressing system, provider, and patient barriers to hypertension prevention and control by integrating individual strategies previously proven effective (Table 1). The CPHCs will be randomized to either the intervention or control group. In the CPHCs assigned to the intervention group:

• Physicians will receive training in the use of treatment algorithms based on hypertension guidelines, including both pharmacologic and non-pharmacologic components, through an online continuing education course. In addition, an on-site intensive training and certification session will be conducted by investigators.

• Community health workers (CHW) will be trained in facilitating behavioral change through BP monitoring, medication management, and lifestyle modifications during a 2-day interactive training session followed by an onsite field testing and certification.
  – CHW will deliver antihypertensive medications to patients’ homes.
  – CHW will serve as a source of education, motivation, and social support, and as facilitators of healthcare utilization for patients and their families.
CHW will conduct home visits, schedule appointments with primary care physicians, and provide tailored counseling to address barriers to hypertension self-management and effectively change behaviors.

- Individualized text messages to promote lifestyle changes and alerts/reminders to reinforce medication adherence will be sent out weekly from an information technology platform at IECS.

Clinics randomized to the control group will continue with usual care.

6.A. Theoretical Framework

Our comprehensive hypertension intervention incorporates elements of the Chronic Care Model (CCM)\(^{112,113}\) and a behavioral framework that includes components of social cognitive theory\(^{114}\) and the transtheoretical model\(^{115,116}\) to tailor the intervention to each participant. CCM emphasizes the importance of chronic disease management from within the framework of the primary care setting and incorporates the primary care physician, patient, and patient’s community. Social cognitive theory emphasizes goal setting, modeling behavior after others, self-efficacy and social support for behavioral change. The transtheoretical model recognizes that patients are at different levels of willingness to change behavior and have different barriers to behavior change, which stresses the importance of tailoring interventions to the patient. Intervention strategies that are congruent with these theoretical foundations have been successfully used in previous trials\(^ {61-64}\).

6.B. Physician Intervention

6.B.1. Physician Education

The Remediari+Redes program conducts continuing medical education which is required by multiple medical societies in Argentina as part of their certification/re-certification. We will partner with them to enroll physicians working in the intervention CPHCs in our education program.

The education program will consist of:

- An online continuing education course on hypertension management for primary care physicians
- An on-site intensive training and certification session by investigators
- Additional distance learning re-training modules for annual recertification

These workshops and courses will focus on:

- Standard treatment algorithms for stepped-care management of hypertension based on the latest report of the Joint National Committee and the Latin American Guidelines on Hypertension, including material developed by the Directorate of NCD of the Ministry of Health\(^4,117\)
- Education will include both lifestyle modifications (weight loss, sodium reduction, physical activity, moderation of alcohol intake, potassium rich and DASH diet) and pharmacologic treatment (assess CVD risk factors and absolute risk, treatment algorithm, initial drug choices, stepped-care approach to titrating medications, and follow-up visits) components
- Strategies to improve medication adherence will be emphasized, including discussing sexual dysfunction and other medication side effects that could impact adherence with patients during clinic visits.
Table 1. Strategies to Overcome Barriers to Hypertension Prevention and Control

<table>
<thead>
<tr>
<th>Barrier</th>
<th>General approach</th>
<th>Specific strategy to overcome barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systems Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient time</td>
<td>Team change</td>
<td>• Simplify the physician’s task</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Assign some responsibility for TLC to CHW*</td>
</tr>
<tr>
<td>Lack of reimbursement for TLC counseling</td>
<td>Team change</td>
<td>• Assign some responsibility for TLC to CHW</td>
</tr>
<tr>
<td>Lack of continuity of care</td>
<td>Team change</td>
<td>• CHW facilitates physician appointments</td>
</tr>
<tr>
<td>Lack of continuity of care</td>
<td></td>
<td>• Leverage clinical network to negotiate pharmaceutical prices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Work with the Remediar+Redes program to provide additional antihypertensive medications</td>
</tr>
<tr>
<td>Limited free medications</td>
<td>Policy change</td>
<td>• Provide automated home BP monitor and BP log to patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Provide home BP monitoring records to physicians at clinical visit</td>
</tr>
<tr>
<td><strong>Provider Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of adherence to treatment guidelines,</td>
<td>Physician education</td>
<td>• Interactive, case-based workshops delivered by opinion leaders following adult learning theory</td>
</tr>
<tr>
<td>“clinical inertia”</td>
<td></td>
<td>• Pocket card with guidelines as decision tree</td>
</tr>
<tr>
<td>Uncertainty that office BP represents usual</td>
<td>Home BP monitoring</td>
<td>• Provide automated home BP monitor and BP log to patients</td>
</tr>
<tr>
<td>BP represents usual BP</td>
<td></td>
<td>• Provide home BP monitoring records to physicians at clinical visit</td>
</tr>
<tr>
<td><strong>Patient Level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor adherence to medications</td>
<td>Reminding,</td>
<td>• Text reminders to reinforce adherence to medications</td>
</tr>
<tr>
<td></td>
<td>Family-support,</td>
<td>• Family members help remind each other</td>
</tr>
<tr>
<td></td>
<td>Patient education,</td>
<td>• Provide pill box and review medications</td>
</tr>
<tr>
<td></td>
<td>Home BP monitoring</td>
<td>• Self-monitoring provides immediate feedback</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Screen for depression and alcohol dependency</td>
</tr>
<tr>
<td>Hypertension knowledge/ risk perception</td>
<td>Patient education</td>
<td>• Information on importance of maintaining BP control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Counseling tailored to individuals’ risk factors</td>
</tr>
<tr>
<td>Poor memory</td>
<td>Reminding,</td>
<td>• Text reminders to mobile phone or email</td>
</tr>
<tr>
<td></td>
<td>Family support,</td>
<td>• Family members help remind each other</td>
</tr>
<tr>
<td></td>
<td>Patient education</td>
<td>• Provide pill box and review medications</td>
</tr>
<tr>
<td>Low health literacy</td>
<td>Patient education</td>
<td>• Transmit consistent, clear messages for TLC</td>
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<tr>
<td></td>
<td></td>
<td>• Recruit CHW from local community to ensure that health information is culturally and linguistically appropriate</td>
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<tr>
<td>Poor motivation</td>
<td>Reminding,</td>
<td>• Use motivational interviewing to tailor intervention</td>
</tr>
<tr>
<td></td>
<td>Family-support,</td>
<td>• Tailor text/email reminders to reinforce behavior change</td>
</tr>
<tr>
<td></td>
<td>Patient education</td>
<td>• Family support for TLC</td>
</tr>
<tr>
<td></td>
<td>Home BP monitoring</td>
<td>• Self-monitoring provides immediate feedback to reinforce TLC</td>
</tr>
<tr>
<td>Medication costs</td>
<td>Policy change,</td>
<td>• Leverage clinical network to improve price and access</td>
</tr>
<tr>
<td></td>
<td>Physician education,</td>
<td>• Train physicians to prescribe free and low cost generic medications</td>
</tr>
<tr>
<td></td>
<td>Patient education</td>
<td>• Successful TLC may decrease need for medication</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Physician education,</td>
<td>• Discuss any medication adverse effects with providers</td>
</tr>
<tr>
<td></td>
<td>Patient education</td>
<td>• Screen for depression and refer for care</td>
</tr>
</tbody>
</table>

*TLC = therapeutic lifestyle change; CHW = community health worker
• An interactive case-based curriculum in line with adult learning strategies will be utilized with certificates of completion provided at the conclusion of the training workshops.

In addition, laminated pocket-cards summarizing the evaluation and treatment algorithm set forth in the guidelines and formatted as a decision-tree will be provided to each participating physician.

6.B.2. Blood pressure audit and feedback

Primary care physicians will review home blood pressure measurements recorded by community health workers. If average home systolic blood pressure is \( \geq 140 \text{ mm Hg} \) or diastolic blood pressure is \( \geq 90 \text{ mm Hg} \), a clinic visit should be scheduled. In addition, if patients’ blood pressure measurements at the month 6 or 12 nurse data collection home visits are \( \geq 140/90 \text{ mm Hg} \), based on feedback from monthly quality control reports, a clinic visit should be arranged. At the clinic visit, patients’ blood pressure will be rechecked. If the blood pressure treatment goal is not achieved, an additional class of antihypertensive medication should be added or the medication dose should be titrated according to the hypertension management algorithm.

6.C. Community Health Worker Home-based Intervention

The patients’ and their family members’ education will be delivered by CHW in the participants’ homes. The CHW will visit participants’ home monthly during the first 6 months (intensive intervention) and bimonthly after 6 months (maintenance). The family-based intervention will start with an initial 90 minute home visit led by a CHW at a time when all family members in the household can be present. Subsequent 60 minute monthly or bimonthly follow-up visits to provide training and support on medication adherence, BP self-monitoring, and lifestyle modification will also be conducted by the CHW. Antihypertensive medication will be delivered to patients who had poor adherence to medication by CHW at home visits according to physician’s prescription schemes. The CHW will also check for medication adherence and answer questions about side effects. Home visits will also focus on social support, specific behavior change goals, problem solving, and maintaining motivation during challenging situations.


In this implementation research, we will use publically available materials from NIH, CDC, and other resources. These materials will be translated into Spanish.

- **Blood Pressure Lowering Packet** – Participants will be provided with a packet for the lifestyle intervention containing the Spanish version of NHLBI’s *Keep the Beat: Control Your High Blood Pressure*. It contains information about BP, healthy weight, physical activity, heart healthy eating, dietary sodium reduction, alcohol moderation, and BP drug adherence. This packet will also provide culturally appropriate low-sodium DASH recipes, a log for monitoring weight, a form to help patients remember questions they have for their physician between appointments and other supplemental resources developed by NIH or CDC.

- **Blood Pressure Monitoring Device** – Each family will receive an Omron HEM-737 BP monitor with appropriately sized cuffs for each adult family member’s arm circumference. Written instructions and the users’ manual for the BP monitoring device will also be provided.

- **Blood Pressure Log** – A self-monitoring tool in which participants record their BP measurements weekly using the Omron HEM-737 device will be provided. Additionally,
non-hypertensive family members will monitor and record their BP every 6 months.

- **Pill Box and Medication Table** – Each participant will receive a pill box to aid in medication management. A culturally adapted version of the American Heart Association’s *How Do I Manage My Medicines?* will also be provided that includes a table for recording all medications, doses, and time to take each medication to aid in managing multiple medications.

### 6.C.2. Home delivery of antihypertensive medications

For study participants who have poor adherence to treatment or have difficulty in obtaining prescription drugs, the CHW will pick up antihypertensive medications at the pharmacy and delivery them to study participants’ homes monthly or bimonthly during home visits.

### 6.C.3. Antihypertensive medication adherence

The goal of the intervention is to have participants adhere to the prescribed medications. CHWs will explain the purpose and importance of medication adherence to participants. CHWs will address possible barriers to medication adherence, such as side effects and forgetting to take medication, with participants. CHWs will discuss the importance of talking to a health care provider about side effects, as well as any other questions participants might have about their BP and medications. Recommendations will be provided to help participants remember to take their medications, including putting medications near their toothbrush, setting up a buddy system with someone else who takes daily medication, and putting reminder notes in visible locations. Weekly pill boxes will be provided to all participants to aid in medication management. CHWs will work with participants to fill in the medication table with all prescribed medications, doses and times of administration. The table will be used to fill the pill box with weekly medication.

### 6.C.4. Home blood pressure monitoring

Each family will receive an Omron HEM-737 BP monitor and appropriately sized cuffs to accommodate adult family members. Participants will be given a log to record BP readings on a weekly basis for those with hypertension and every six months for non-hypertensive family members. The CHW will instruct the family in how to use the BP monitoring device at the initial visit based on American Heart Association Guidelines, including resting seated for 5 minutes prior to monitoring, abstaining from smoking, drinking, and exercise 30 minutes prior, and recording three measurements each time the monitor is used. On subsequent monthly visits the CHW will review the log with the participants and encourage continued proper use.

### 6.C.5. Lifestyle modification

#### 6.C.5a. Goals of Lifestyle Intervention

This multicomponent lifestyle intervention program is based on lifestyle modifications for BP prevention and control in the Joint National Committee, which recommends weight loss if overweight, limiting sodium and alcohol intake, regular physical activity, and adopting a DASH diet. The specific intervention goals are:

- Reduce weight by 5 kg (11 pounds) or more if overweight
- Maintain weight if normal weight
• Limit daily sodium intake to 100 mmol or less (equivalent to 6 g/day sodium chloride or 1 teaspoon of table salt)
• Engage in moderate physical activity 2.5 hours a week or more
• Reduce alcohol intake to no more than two drinks a day for men and one drink a day for women
• Recommend a DASH-style diet high in fruits, vegetables, and low-fat dairy and low in fats and cholesterol
• Take medications as prescribed

6.C.5b. Reduce sodium intake

The goal of the sodium intervention is to help participants reduce sodium intake to 100 mmol per day or less, equivalent to 6 g/day of table salt (sodium chloride). Key curriculum content and behavioral strategies include identifying the sodium content of foods using nutrition labels and guides, and devising sodium reduction strategies. The latter include: finding sodium-modified food products, substituting different items for very high sodium foods, learning to make more appropriate food choices in restaurants, reducing salt use when cooking, and adapting taste preferences. The families will be encouraged to remove salt shakers from the table, use less salt in cooking, and buy less canned and processed foods to reduce sodium intake.

Taking advantage of the Ministry of Health’s agreement with food industry and the federation of bakeries to cut salt consumption by 15% in processed foods and 40% in breads by 2014, families will be taught to reduce sodium by reading labels and choosing low sodium options at the store.

6.C.5c. Increase physical activity

The goal of the physical activity component in the intervention program is to engage in moderate physical activity at least 2.5 hours per week. Examples of moderate physical activity and suggestions for adding physical activity into daily life are provided in the educational materials. The intervention focuses on helping participants determine how best to fit physical activity into their lives and takes into account each participant’s initial motivation, current activity patterns, and intensity desires. Home visits will include information and behavioral skills relevant to the physical activity component of the intervention. Specific behavioral strategies for increasing physical activity include identifying pleasurable activities for participants, self-monitoring physical activity patterns, scheduling daily time to be physically active, goal-setting, identifying barriers to physical activity, and problem-solving in order to develop specific strategies in dealing with barriers.

6.C.5d. Limit alcohol intake

The goal of the alcohol intervention is to limit alcohol consumption to no more than 2 drinks per day for men and no more than 1 drink per day for women. Participants will receive information on the health effects of alcohol, maximum target alcohol consumption levels, and how much alcohol constitutes a drink.

6.C.5e. Reach/maintain a healthy weight

The goal of the weight-loss portion of the intervention programs is to help participants who are overweight (BMI ≥ 25) lose 5 kg (11 lb) or more and maintain this weight loss for the duration of the
trial. Specific strategies for weight loss include:

- self-monitoring of diet and physical activity
- development of personalized dietary and physical activity plans
- moderate caloric reduction
- increased physical activity
- identifying problematic situations for undesired behavior and developing and rehearsing specific plans of action to deal with those situations
- developing core food-choice competencies, and
- reducing portion sizes, substituting alternative foods, and modifying the original items to be lower in calories.

CHWs will teach participants shopping and healthy cooking based on the DASH diet plan. For those with a BMI below 25, the intervention focuses on preventing weight gain by adopting the DASH diet and participating in regular physical activity.

6.C.5f. Adopt a healthy eating plan based on the DASH diet

The DASH diet promotes low-fat dairy products, fish, poultry, and lean meats to reduce total fat, saturated fat, and cholesterol and increase protein and calcium. It includes fruits and vegetables to increase potassium, magnesium, and dietary fiber. For an intake of 2000 kcal/day, this dietary pattern contains approximately four to five vegetable servings, four to five fruit servings, seven to eight servings of grains and grain products, two to three servings of low-fat dairy products, and two or fewer servings of meat, poultry, or fish.

Three specific dietary goals are emphasized during home visits in order to achieve the DASH dietary pattern:

- reduction of total and saturated fat will be emphasized by focusing on reduced consumption of red meat and regular-fat dairy products
- eat 9-12 servings of fruits and vegetables per day; and
- eat two to three servings of low-fat dairy products per day

These goals are critical because each represents a key aspect of the DASH dietary pattern. In order to switch to the DASH eating plan, CHWs will explain the diet to participants and will encourage them to think of ways they can incorporate the DASH diet into their usual diet. If they have trouble making dietary changes, the CHWs will provide the participants with a food diary where they can record everything they eat for several days and identify eating patterns where they could start making changes to increase fruits and vegetables and low fat dairy products and decrease fat intake.

CHWs will use a number of strategies and recommendations to incorporate these dietary components into the participants’ daily eating pattern. For example, the fruit and vegetable pattern can include two to three servings of fruit at breakfast, typically juice and another serving of fruit, perhaps with cereal. Lunch can include three to four servings of fruit and vegetables such as soup, salads, sandwiches, juice, and fruit as dessert. Dinner can include three to four servings of fruits and vegetables. Large salads can be a part of
many meals, as well as raw vegetables for pre-meal items and one to two fruits or vegetables as snacks. Participants can also increase the portion size of vegetables to increase the number of servings. Setting goals for meals, focusing on key fruits and vegetables for additional consumption goals, and increasing portion sizes are strategies that have been successfully used in previous fruit and vegetable intervention programs. In addition to emphasizing fruits and vegetables, CHWs will also emphasize low-fat dairy products, such as low-fat or skim milk, low/non-fat yogurt, and low-fat cheeses, as well as limited portions of lean cuts of beef, chicken, and fish.

6.C.5. Educational counseling

CHW will use educational counseling techniques to identify barriers to behavioral change and help participants set goals.

Family members will be encouraged to support and be accountable to each other in making lifestyle changes, taking medications, and monitoring BP. We will develop culturally appropriate patient education materials based on NHLBI’s BP lowering guides.

6.D. Mobile health (mHealth) intervention

We will develop individualized messages using educational materials and information provided by the CHWs on participants’ intervention priorities at baseline and follow-up visits. These messages will also be tailored to hypertension status and perceived barriers to behavior change identified via educational counseling. The messages will consist of motivational statements aimed at overcoming perceived barriers and behavior-change techniques to reinforce the in-person educational intervention. For example, in the case of a participant with hypertension on medication, a text message reminder to take antihypertensive medications first thing in the morning may be sent. In the case of a sedentary family participant, a text message providing examples of physical activity such as dancing at home to a favorite tune may be sent. Text messages will be sent from a technological platform at IECS to participants and family members using a 1-way outgoing message system.

CHW will obtain information about BP levels and barriers to adopting the intervention for each participant during monthly home visits, record this information on the CHW visit form, and provide it to the project coordinator, so that appropriate text messages can be sent. Many tested and culturally-appropriate messages from an on-going NHLBI-sponsored clinical trial of a mobile health intervention for hypertension prevention in Latin America can be used in the intervention.

6.E. Community Health Workers

CHW will attend a two day training course including educational counseling techniques, measuring BP, the Stages of Change Model, medication management, and culturally appropriate behavioral change related to hypertension based on the CDC’s The community health worker’s sourcebook: A training manual for preventing heart disease and stroke and NHLBI’s Your heart, your life: A community health worker’s manual for the Hispanic community. Retraining and certification of CHWs will be conducted every six months.

CHW will visit each family’s home for an initial 90 minute visit and subsequent 60 minute monthly follow-up visits to provide training and support on lifestyle modification, medication adherence, and BP self-monitoring. In order to increase medication adherence, CHW will also supply hypertensive family
members with pill boxes, review prescribed medications with patients, and demonstrate proper pill box use. CHW will also help to schedule medical appointments for patients with their primary care physician as needed or at least every 6 months.

6.E.1. Community health worker training

6.E.1a. Educational counseling and stages of change model

CHWs will be taught to do educational counseling in order to encourage study participants to change behavior by increasing self-efficacy and employing methods to elicit a desire or readiness to change from participants. They will also be taught the concepts for the stages of change model that presents five possible stages according to participants’ willingness to change their behavior - pre-contemplation, contemplation, action, maintenance, and relapse. At each stage of change, educational counseling can be used to help participants move toward the action stage. CHW will receive training and practice identifying participants’ stage of change and educational counseling techniques. Our previous mHealth trial used interviewing techniques to encourage behavior change, and the training materials used in that trial can be adapted for use in the CHW training.

6.E.1b. Culturally appropriate behavioral change for hypertension

Select sections from the CDC’s The community health worker’s sourcebook: A training manual for preventing heart disease and stroke and NHLBI’s Your heart, your life: A community health worker’s manual for the Hispanic community has been culturally adapted for Argentina and will be used to provide training to CHW on hypertension and appropriate lifestyle modifications. Training sessions include a combination of instructor presentations and activities for the trainees. Handouts will be provided so community health workers can continue to review the material on their own and share appropriate materials with study participants. The following five behavioral change training sessions will be conducted for community health workers:

1) The high blood pressure training provides an explanation of high BP and the causes, measurement, treatment and control, and medications that can be prescribed for high BP. Handouts include a step-by-step guide to how BP is measured, an explanation of BP numbers, questions for patients to ask their doctors about their BP, steps to take to prevent and lower high BP, and ways CHW can support participants with high BP. Activities during this session include a discussion of ways to prevent and control high BP and instruction, demonstration, and practice monitoring BP using home BP monitoring devices (see section 6.C.3 for details on home BP monitoring).

2) The session on healthy eating and weight control will instruct participants on why weight control is important for health, weight loss methods, how to help other make healthy food choices, reading labels for nutritional information, and the DASH eating plan. Materials provided include a BMI chart for determining healthy weight, overweight, and obesity, information on energy balance, weight loss tips, tips for heart-healthy eating at restaurants, suggested daily calories, sodium content of foods, tips to eat less sodium, spice suggestions for use in place of salt, a guide to reading food labels, suggested serving sizes, details of the DASH eating plan, and
tips for CHW’s to talk to study participants about healthy eating and weight loss. Activities during this session include instruction, demonstration, and practice measuring body weight.

3) **Physical activity** training includes the importance of physical activity, basics of an individual physical activity program, recommended amounts of physical activity, the relationship between physical activity and weight loss, ways to motivate participants to be more active, and ways communities can be more supportive of physical activity. Handouts for this training include a worksheet to develop a personal physical activity plan, a calendar for recording physical activity, tips for adding physical activity to daily life, examples of activities at different intensity levels, stretching exercises, and a sample walking program. Discussion during the session will center around what CHWs believe are barriers to physical activity and ways they believe they can get people in their communities to be more active.

4) The training session on **taking medicine** will focus on the importance of taking medicine as prescribed by the doctor, informing the doctor of other medications the patient takes, identifying ways patients can remember to take their medicine, encouraging patients to ask the doctor, nurse or pharmacist any questions they have about their medications, and exploring how community health workers can help people overcome barriers to medication adherence. CHWs will be provided with tips to help participants get and take their medications and the American Heart Association guide to managing medicines. During this session community health workers will be trained to guide participants through the use of pill boxes to manage medications (see section 3.F.4b for details on pill box medication management).

5) The **talk to your doctor** training will give CHWs the tools to get the most out of their appointments with their primary care physicians. The training will include the patient’s role and responsibilities as a member of their healthcare team, how the patient should prepare for a doctor’s visit, things they should do during the visit, and instructions for patients to have emergency information in a convenient place in the event of an emergency. CHWs will be trained to encourage patients to ask questions at physician appointments, provide an honest and complete medical history and list of medications, and bring a notebook to record important things the doctor says during the visit. Handouts for the session are a daily health diary to be completed by the patient, a guide to asking questions about your health, and a worksheet to record emergency information. During this session, CHWs will discuss and brainstorm ways CHWs can help prepare patients for doctor’s appointments.

6.E.2. **Responsibilities of community health workers**

6.E.2a. **CHW home-based intervention visits**

1) The **first home visit**: The first home visit will last for approximately 90 minutes. During the first home visit, CHWs will distribute a packet of materials to each family that includes NHLBI’s *Keep the Beat: Control Your High Blood Pressure* adapted for use in Argentina and some supplemental resources useful for lifestyle change. The guide includes helpful information on hypertension, physical activity, heart healthy eating, reducing salt consumption, nutrition labeling, antihypertensive medications, a list of helpful reminders for lowering blood pressure, and questions to ask a physician. In addition, the packet will include a log for monitoring BP, a
log for monitoring weight, a table for organizing medications, and a form to help participants remember questions they have for their physicians between appointments. The CHW will also provide the family with a pill box and a BP monitor. At the first visit, the CHW will go through the packet with the family. They will also show the family how to monitor BP and use the medication management tools. The CHW will take an initial body weight measurement and help participants record their weight in the log. The CHW will use educational counseling techniques to identify participant barriers to behavior change and set realistic goals.

2) **Follow-up home visits**: The follow-up monthly or bimonthly home intervention visits will last for approximately 60 minutes. At each monthly follow-up visit, CHWs will interact with participants using educational counseling techniques to identify barriers to change, review the BP log and monitoring technique, and address any concerns or questions from participants. CHWs will record goals and barriers identified during each visit on the visit form in order to tailor the mobile health intervention. The CHWs will tailor intervention strategies at the follow-up visits based upon individual successes and barriers. During home visits, the CHW will deliver antihypertensive medications to study participants who have poor adherence to treatment or have difficulty obtaining medications by themselves. CHWs can provide additional materials and tools from their training sessions to participants to help them overcome barriers and also promote discussion with participants to help them identify lifestyle modifications that will work to meet the goals of the intervention. They will record the prior month’s BP values. CHWs will also work with participants to set up doctor’s appointments and prepare for them by creating a list of questions to ask the doctor and addressing any concerns participants might have.

**6.E.2b. Teaching participants to monitor blood pressure**

CHWs will train participants to use home BP monitors based on American Heart Association recommendations for the use of home BP monitoring devices. CHWs will advise patients to measure their BP once a week in the morning before taking their medications. They will be advised not to smoke, drink coffee or exercise for 30 minutes prior to using the monitor. The participants will be instructed to sit with their feet flat on the floor and arm resting on a flat surface and to only conduct monitoring after resting seated for five minutes. Three measurements will be taken each time with at least one minute between readings. CHWs will provide participants with a log for keeping track of weekly BP readings, and will review the log and the technique of participants at subsequent home visits.

**6.E.2c. Medication management**

CHWs will provide each participant with a pill box as an aid in medication adherence. Using the American Heart Association worksheet on managing medicines, the CHW will help the participants fill in all their medications, doses, and when to take them into the table. Then the CHW will help the participants use the table to fill the pill box with a week’s worth of medicine. On subsequent visits, CHWs will answer any questions or address any challenges of pill box use or the medicine table with the participants.

**6.E.2d. Medical appointment scheduling**
CHWs will help to schedule appointments with primary care physicians for participants at the patient’s request, the physician’s recommendation, or at least every six months. In addition, prior to the appointment, the CHW will work with participants to ensure they are prepared for the appointment with any questions, description of symptoms, or new medications to report to the physician.

6.E.3. Community health worker home visit content

All home intervention visits are structured to be very interactive with family member input to promote problem solving, support, and program ownership.

6.E.3a. Initial intervention home visit

The initial session will be led by the CHW and will consist of:

1) Verification of contact information
2) Main content area training in which the CHW will go through the BP lowering packet with participants and families to discuss recommended lifestyle modifications
3) BP self-monitoring training
4) Medication management and pill boxes
5) Measurement of participant’s body weight
6) Identification of barriers to change, opportunities for improvement, and goal setting using educational counseling techniques
7) Schedule next home visit

6.E.3b. Monthly follow-up home visit

Monthly follow-up sessions will be led by the community health worker and will consist of:

1) Verification of contact information
2) Review of progress and challenges since last session
3) Review of BP log and monitoring techniques if appropriate
4) Delivery of antihypertensive medications to study participants if needed
5) Review of medications, side effects, management
6) Measurement of participant’s body weight
7) Supplemental instruction and tools on content area training if necessary
8) Identification of barriers to change, opportunities for improvement, additional support needed from the CHW, goal setting, and action plans using educational counseling techniques
9) Check with participants about need for scheduling and/or planning for upcoming physician appointments
10) Schedule next home visit

6.F. Preliminary Formative Research

Before the intervention begins, in depth interviews will be conducted in focus groups of hypertensives and their family members to explore their knowledge, beliefs, and perceptions about hypertension, risk factors, consequences, and barriers to lifestyle changes and pharmacological treatment. In addition, they
will be asked about their familiarity with cell phones, their ability to read and send text messages, and any barriers they can identify that would hinder the mHealth interventions. The results of these focus group interviews will be used to design the intervention to be as effective as possible.

6.G. Cultural Adaptation of the Intervention

All medication management, lifestyle modification, and other interventions will be adopted in order to be appropriate for the Argentine population, a group at high risk for hypertension. The investigator group and consultants on this project have extensive experience with clinical research in South American populations. Previous studies have led to the identification of the following strategies that are incorporated into the design. Most if not all of these strategies are effective and important for all study participants. These strategies include: 1) adequate South American representation at all levels of implementation (i.e., interventionists, investigators, etc.); 2) social support systems for participants; 3) effective communication; 4) involvement of family and community; 5) participant identification with study goals; and 6) food guides and other intervention materials that are consistent with the cultures represented among study participants.

6.H. Integration with Other Disease Management Programs

Training and instruction on medication adherence will apply to all medications participants are prescribed, not just antihypertensive medications. CHWs will review medication lists with participants and their family and demonstrate the use of a pill box, which will assist participants in the management of antihypertensive and other medications.

6.I. Sustainability of Intervention

Sustainability of the intervention encompasses both the long-term incorporation of our program within the primary health care network and sustaining the effects of behavior change among patients and providers. Several elements have been identified as important for sustaining interventions, including infrastructure. The team change model, in which CHW are assigned some responsibility for supporting and promoting behavioral change, provides a sustainable infrastructure for ongoing intervention. The presence of leadership support is another key factor in sustaining organizational change. We have demonstrated support from the Ministry of Health which maintains the primary health care network, the Remedia+Redes program, in Argentina. A successful intervention will be disseminated and scaled-up throughout the clinics in the network to improve hypertension prevention and treatment network-wide (see section II).

7. Study Outcomes

7.A. Primary Outcome

The net change in SBP and DBP over the 18-month intervention among hypertensive participants is the primary outcome. The net change is defined as the difference between the intervention and control groups in BP changes from baseline to termination of the intervention.

7.B. Secondary Outcomes

The secondary outcomes include:

- Proportion of hypertension control (BP<140/90 mmHg) among hypertensive patients
• Self-reported medication adherence among hypertensive patients
• Cost-effectiveness of the intervention
• Net change in SBP or DBP among normotensive participants
• Net change in body weight and waist circumference
• Increase in number of primary care visits resulting in intensity of treatment

Other outcomes include changes in physical activity and diet.

8. Study Visits and Data Collections

Study nurses will conduct screening and baseline visits for all study participants in their homes. The follow-up visits at months 6, 12, and 18 (termination visits) will also be conducted in participants’ homes by study nurses. The primary purpose of these home visits is to collect study data without requiring participants to come into the clinic and increase follow-up rates. At these visits study nurses will collect all study data using questionnaires and standardized measurement methods.

CHW will conduct additional monthly home visits for only participants recruited from intervention clinics. These visits will be separate from those of the study nurses. The primary purpose of these visits is to deliver the trial intervention (see section 6.C).

8.A. Study Data Collection Visits

After brief telephone or in-person prescreening, eligible participants and their adult family members will be scheduled for screening/baseline visits. All study visits will occur in the homes of the study participants where study nurses will collect all study data. The study data collection schedule is given in Table 2. Data will be entered centrally at IECS using OpenClinica.

8.A.1. Screening visit

The purpose of the screening visit is to identify and confirm patients’ eligibility for, and interest in, the proposed study.

8.A.2. Baseline visits (BV)

The purpose of the baseline visits is to obtain informed consent, relevant medical history, and BP measurements. A consent form approved by the Institutional Research Boards (IRB) of each institution will be used to obtain informed consent by the study nurse. The two screening/baseline visits will be between 1 and 14 days apart. The reason for two visits at baseline is to obtain repeated BP measurements at two separate occasions. Three BP readings will be obtained at each visit. In addition, heart rate, height, weight, and waist girth will be measured by study nurses using standard procedures. Body-mass index (BMI) will be calculated. Brief information on medical history (including use of antihypertensive medication), cigarette smoking, alcohol drinking, diet, and physical activity will also be obtained.

8.A.3. Follow-up and termination visits

<table>
<thead>
<tr>
<th>Measures</th>
<th>BV1</th>
<th>BV2</th>
<th>Follow-up visits, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BP medication</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BMI and WC</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Clinical lab</td>
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<td></td>
<td>X</td>
</tr>
</tbody>
</table>

BV = screening/baseline visits; BMI = body mass index; WC = waist circumference; TV = termination visits at month 18
Follow-up visits will be scheduled 6, 12 and 18 months following the screening/baseline visits. Two termination visits will be scheduled in month 18 to obtain the end-study BP measures on 2 separate occasions. Three BP readings, heart rate, weight, and waist girth will be obtained at each follow-up visit. Updated information on the use of antihypertensive medications, cigarette smoking, alcohol drinking, diet, physical activity, and health care utilization will also be obtained.

During clinic visits for patient care, serum lipids, plasma glucose, and other clinical lab measurements will be obtained based on hypertension management guidelines and the Remediar+Redes program reimbursement policy. These measurements will be used for patient care. However, they also provide indicators of co-morbid conditions.

8.B. Study Measurements

8.B.1. Questionnaire

The study nurses will administer questionnaires obtaining contact information, information on history of hypertension, other CVD risk factors, and health behaviors (e.g., smoking, alcohol drinking, diet, and physical activity) of participants at the screening/baseline and follow-up visits. Detailed information on adherence to antihypertensive medications, health facility utilization, and costs will be collected. Validated questionnaires will be used for contact information, personal and medical history, socio-demographic information, and utilization of health services. In addition, the IPAQ will be used for physical activity and the Morisky questionnaire will be used for adherence.

8.B.2. Blood pressure

Three BP measurements will be obtained at each data collection visit by study nurses who are masked to clinic assignment. BP will be measured according to a standard protocol recommended by the American Heart Association. BP will be measured with the participant in a seated position after 5 minutes of quiet rest. In addition, participants will be advised to avoid alcohol, cigarettes, coffee/tea and exercise for at least 30 minutes before their BP measurement. A auto-BP cuff (Intellisense Digital Blood Pressure Monitor; model: OMRON HEM-907 XL) will be used and one of four cuff sizes (pediatric, regular adult, large or thigh) will be chosen on the basis of each participant’s arm circumference. Standardized procedures will be used to reduce measurement error. These include protocols for preparing and positioning subjects; selecting an appropriate cuff; imposing restrictions on alcohol and smoking for a specified time period before BP measurement; and maintaining and calibrating all equipment.

8.B.3. Anthropometric measures

During nurse home visits, trained staff will take anthropometric measurements on individuals in light clothing without shoes using a standard protocol. The nurses will bring a tape measure, scale, and portable stadiometer to the home visits.

- Body weight will be measure to the nearest 0.1 kg on a dedicated scale that will be calibrated weekly. Two replicated measurements of body weight will be collected and the arithmetic mean will be used for analyses.
- Body height will be measured to the nearest 0.1 cm with a free-standing stadiometer. Study nurses will employ a standardized protocol and the arithmetic average of 2 measurements at each study visit will be used in analyses. BMI will be calculated as an index for overall obesity.
Waist circumference will be measured (at the smallest circumference between the ribs and the iliac crest) in centimeters to the nearest 0.1 cm. To minimize measurement error, the Gulick II tape measure (Gays Mills, WI) with a no-stretch, retractable tape and tensioning device will be used. Two measurements will be obtained and the arithmetic mean will be used for analyses.

9. Quality Assurance and Quality Control

The quality assurance and control process will be employed at every step of the study.

9.A. Manual of Procedures

We will develop a manual of procedures (MOP) for data collection using the standardized approaches in our study. The MOP will describe the procedures for staff training; participant recruitment; instructions for all forms and procedures; physician and patient education, lifestyle intervention coaching, self-BP monitoring methods, and text/email message delivery; and other operational aspects of the study.

9.B. Training and Certification

All study personnel will be required to participate in a study training session prior to the initiation of any study procedures. The training sessions will include all aspects of the protocol and MOP with regard to recruitment, follow-up visits intervention protocol, and measurement procedures. Special attention will be paid to training community health workers in family-based strategies for lifestyle change, medical adherence, self-BP monitoring methods, and educational counseling to encourage behavioral change. Periodic retraining sessions will be conducted subsequently to maintain standard application of all study-related procedures. Study nurses will receive annual training at the participating clinic, and CHWs will receive training and re-certification every six months at the clinics over the course of the study.

9.C. Site Visits

Investigators and staff from SDCC and FCC will travel to each participating CPHC to assess adherence of clinical staff to the study protocol and MOP. These visits will provide opportunities to discuss and evaluate solutions related to issues that are critical to the study and will be conducted at least once per year.

9.D. Quality Monitoring and Reporting

A quality control (QC) subcommittee will review the QC data regularly, including timeliness and completeness of study visits and data collection, intervention protocol adherence, and data quality (such as BP digit preference). Reports on data QC will be sent to each CPHC monthly.

10. Statistical Power and Data Analysis

10A. Power and Detectable Differences

The study will use a cluster randomized design; 9 clinics will be assigned to intervention and 9 to control groups. The intervention and follow-up will last for 18 months and the primary outcome is the difference in BP changes between the intervention and control groups. Based on experience from our previous studies and others, the standard deviation of change in SBP over 18 months is approximately 10.0 mmHg.\textsuperscript{134-136}

We calculated the detectable difference in SBP changes between the intervention and control groups at a significance level of 0.05 for a two-sided test with a statistical power of 80% using various sample sizes, intra-cluster correlations, and standard deviation among hypertensive patients (Table 3 and 4). The sample
size calculation used formula developed by Donner and Klar\textsuperscript{137,138} and was implemented in the Power Analysis and Sample Size (PASS 2008) software (NCSS, Kaysville, UT). If we used an intra-cluster correlation coefficient of 0.06 based on data from Dr. Olugbenga Ogedegbe and Dr. Salim Yusuf, which is greater than the upper limit (0.002 to 0.01) recommend by PASS and provides a conservative estimate of sample size,\textsuperscript{139,140} and a standard deviation of 10.0 mm Hg, we will be able to detect a 3.74 mm Hg difference in SBP change among 89 participants (total sample) and 3.86 mm Hg difference in SBP change among 62 participants (hypertensives). These small mean BP differences have important public health implications at the population level\textsuperscript{141,142} and have been widely used as target treatment goals for clinical trials.\textsuperscript{134,136,143-145} To allow for an 85\% follow-up rate, we estimate that each clinic will need 105 participants and each group will need to recruit 945 trial participants. Based on our previous experience, we anticipate a much higher follow-up rate. The above power calculation is based on a two-sample t-test using cluster design. We will utilize mixed-model regression analysis which should increase statistical power because of inclusion of multiple repeated measurements. This sample size ensures adequate power for testing our secondary outcomes as well. For example, we have 80\% power to detect a 18\% increase in hypertension control (from 42\% to 60\%).\textsuperscript{117}

**10.B. Data Analysis Plan**

Intention-to-treat analyses will be conducted, in which the primary and secondary outcomes will be compared between participants according to their randomization assignment, regardless of their actual adherence to the intervention.

**10.B.1. Exploratory Data Analysis**

<table>
<thead>
<tr>
<th>Standard Deviation, mm Hg</th>
<th>Intra-cluster Correlation</th>
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<tbody>
<tr>
<td></td>
<td>0.08</td>
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<tr>
<td>8.0</td>
<td>3.38</td>
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<td>10.0</td>
<td>4.23</td>
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<td>12.0</td>
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<td>14.0</td>
<td>5.92</td>
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<tr>
<td>16.0</td>
<td>6.77</td>
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</table>

* 62 hypertensives and 27 normotensives

Table 3. Detectable Effect Size on Blood Pressure in All Study Participants (1-\(\beta\)=0.80; \(\alpha\)=0.05; number of clusters per group = 9; individuals per cluster = 89*)

<table>
<thead>
<tr>
<th>Standard Deviation, mm Hg</th>
<th>Intra-cluster Correlation</th>
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<tbody>
<tr>
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<tr>
<td>12.0</td>
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<tr>
<td>14.0</td>
<td>6.07</td>
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<tr>
<td>16.0</td>
<td>6.93</td>
</tr>
</tbody>
</table>

* 62 hypertensives

Table 4. Detectable Effect Size on Blood Pressure in Hypertensives (1-\(\beta\)=0.80; \(\alpha\)=0.05; number of clusters per group = 9; individuals per cluster = 62*)
Baseline characteristics of patients (demographics, clinical variables, lifestyle factors, and BP and laboratory measurements) will be compared between the intervention and control groups using one-way ANOVA or $\chi^2$ tests.

10.B.2. Primary Outcome

We will test the research hypothesis that there is a greater reduction in mean BP in the intervention group than in the control group using a mixed effects regression analysis:

$$Y_{ijkl} = b_0 + b_1G_i + b_2C_{ij} + b_3P_{ijk} + b_4T_l + b_5GT_{il}$$

where $Y_{ijkl}$ is BP for the $k$th participant ($P$) nested in the $j$th primary care clinic ($C$) nested in the $i$th intervention group ($G$) at the $l$th time ($T$). $GT_{il}$ is the treatment group × time interaction. Rejection of null hypothesis, $b_5=0$, indicates different slopes ($b_4$) of change between intervention and control groups. Time can also be treated as a categorical variable to assess changes in BP between two groups at different time intervals. In this model, participants and clinics are assumed to be random effects and intervention group, time, and the interaction are assumed to be estimable fixed effects. Although an autoregressive correlation structure is the logical choice for these repeated measures, exchangeable and unstructured correlation structures will be investigated as well. PROC MIXED or PROC GLIMMIX of SAS version 9.2 (SAS Institute Inc., Cary, NC) will be used to obtain point estimates and standard errors of the treatment effects, and to test for differences between interventions.

10.B.3. Secondary Outcome

The secondary outcomes include both continuous and categorical variables. The analyses of the continuous variables will use similar models to those for the primary aim. We will conduct logistic regression analyses for categorical outcomes using SAS PROC GENMOD. Since we are measuring subjects at multiple time points, we will use GEE for these analyses.

10.b.4. Subgroup Analyses

Net reduction in BP will be compared by age (<60 vs. ≥60 years), sex (male vs. female), cardiovascular risk (with vs. without history of major cardiovascular disease, hypercholesterolemia, and diabetes), body-mass index (obesity vs. non-obesity), and number of hypertensive family members (one vs. more than one) in subgroup analyses.

10.C. Cost-effectiveness Analysis

An economic evaluation component based on patient-level trial data will be complemented with a model-based component for long-term costs and effects extrapolation.

10.C.1. Component 1

Trial-based primary economic evaluation will use patient-level data collected from the proposed study.\textsuperscript{148,149} We will document all resources involved in conducting this comprehensive intervention program, as well as all patient-level costs, in 2016 ArgentineanPesos adjusted by Argentina consumer price index (CPI) and then converted into International Dollars (Int$). Primary incremental cost effectiveness ratio (ICER) measure will be cost per mmHg of change in SBP and DBP. Secondary measures will be cost per additional case of hypertension control, per hypertension case avoided, and per QALY using the Argentina Euroqol EQ-5D.\textsuperscript{150} Non-parametric bootstrapping will be used to estimate parameter uncertainty in the trial-
based component (ICER 95% CI, cost-effectiveness scatter-plot and cost-effectiveness acceptability curve). A willingness to pay (WTP) threshold will be set corresponding to 3 times the gross domestic product (GDP) of Argentina in 2016 Int$.

10.C.2. Component 2

A Markov model will be adapted\(^{151}\) and further developed to extrapolate the long-term effects of the proposed program throughout patient’s lifetime (5% annual discount rate for benefits and costs).\(^{152}\) Each cycle will last 6 months, consistent with the study time points. The model will have three health states: (1) The same health state without suffering any CVD events; (2) Have an acute CVD event (CHD, unstable angina, stroke/TIA, HF, and peripheral artery disease); or (3) Die from causes other than CVD. Transition probabilities will be based on the Framingham cohort study general CVD risk equation.\(^{153}\) All patients suffering an acute event could die during that time period (CVD death) or survive (at least for that time period). Every patient that completes one cycle in any state other than death will receive 0.5 years of life saved. CVD risk reduction from improved SBP and DBP will be calculated based on the literature.\(^{154}\) In addition to the program costs, the healthcare costs for each Markov health state will be estimated from a healthcare sector perspective in 2016 Int$. Primary ICER measures will be cost per QALY and life year (LY) saved. We will perform a one-way sensitivity analysis of ICER. In particular, up to a 12% discount rate as suggested by the World Bank\(^ {155}\) and different assumptions of treatment effect durations will be explored. As part of multivariable sensitivity analysis, the trial-based transition probabilities of the Markov health state instead of the Framingham model estimates will be explored till the end of 18 months. Monte-Carlo simulations\(^ {156}\) will be also employed to generate the ICER scatter-plot and 95% CI, and cost-effectiveness acceptability curves for the model-based component.

11. Dissemination and Scale-up Plan

Hypertension imposes not only clinical but also economic consequences to an already overburdened health care system in LMIC, including Argentina.\(^ {132}\) Although CVD is the leading cause of death in Argentina, national health programs and policies are still focused on communicable diseases and perinatal/childhood conditions. Chronic disease prevention and control have been largely ignored. In addition, the healthcare system is biased towards expensive specialist services and high-tech interventions, and overlooks the need for primary care.\(^ {133}\) Therefore, our study will provide an exceptional opportunity for health policy makers, health care providers, and the public to focus on the prevention and control of hypertension and related CVD.

11.A. Dissemination Plan

The dissemination plan is designed to translate and communicate the research findings to inform health policy, health practice, and public opinion. We will publish the study findings in international, national, and local medical and public health journals and make presentations at national and regional medical and public health professional meetings. In addition, we will organize national and regional workshops and use mass media to promote the intervention program proven effective in our study.

11.B. Scale-up Plan

Our study is conceived and planned with the strong support and involvement of the Remediar+Redes program. This national program under the Ministry of Health provides ambulatory drugs free of charge to
almost 7,000 CPHC who care for uninsured poor populations across the country. If proven effective, this program will be implemented throughout the entire Remediar+Redes network in year 5 of this study. Specifically, we anticipate the following scale-up activities:

- Physician education: One of important missions of the Remediar+Redes program is to train and retrain healthcare providers. We will scale-up our healthcare provider training program to the entire network;
- Community health workers: We will work with the Remediar+Redes program to train their community health workers for hypertension prevention and control. We will work with the Ministry of Health to increase the community health worker workforce for chronic disease control;
- Increase number and classes of free antihypertensive medications: Currently, only 3 antihypertensive medications (hydrochlorothiazide, enalapril, and atenolol) are provided by the Remediar+Redes program free of charge. If proven effective, we will encourage the program to provide additional affordable medications to patients;
- Home BP monitoring: If proven effective, we will work with authorities of Remediar+Redes to provide free BP monitors to patients with hypertension.

This study has been endorsed by the highest authorities of Remediar+Redes who have promised to work together with the research team along the different steps of this study, as well as disseminate and further implement the hypertension prevention and control strategies at all primary care clinics in Argentina. We also have support from authorities from the Ministry of Health to implement our intervention strategies throughout other national primary health care networks and systems.

12. Timeline

The entire study will last for 5 years. The first year will be used to finalize the study protocol, develop the manual of procedures (MOP) and data collection instruments, and to train study staff. We will work together with NHLBI Project Scientists and other funded teams as a consortium to develop standard metrics and/or protocols in consultation with national and international investigators, policy-makers, local community leaders, and focus groups. We will use these standardized approaches for data collection in our proposed research. The recruitment of study participants, intervention, data collection, and quality control (QC) will last for 3 years. Data entry and QC will be conducted simultaneously during data collection. The first 6 months of year 5 will be used for data analysis and publication. We will conduct data dissemination and scale-up activities in the last year (Table 3).

<table>
<thead>
<tr>
<th>Table 3. Timeline and tasks</th>
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<tbody>
<tr>
<td><strong>Tasks</strong></td>
</tr>
<tr>
<td>Protocol, MOP, forms, training</td>
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<tr>
<td>Recruitment</td>
</tr>
<tr>
<td>Intervention and data collection</td>
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<tr>
<td>Data entry and QC</td>
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<tr>
<td>Analysis and publication</td>
</tr>
<tr>
<td>Dissemination and scale-up</td>
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</tbody>
</table>
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