Ethics Institutional Committee (CIE) of INCAP
Research Protocol

INCAP Investigators:
Manuel Ramírez-Zea, Paola Letona, Julissa Salguero

Investigators from other institutions:
Adolfo Rubinstein, Institute for Clinical Effectiveness and Health Policy – IECS, Buenos Aires, Argentina
Jaime Miranda, Universidad Peruana Cayetano Heredia, Lima, Perú
Homero Martínez, RAND Corporation, Santa Monica, California, USA

Study title (version #2, submitted on 3/14/2011):
Use of mobile technology to prevent progression of pre-hypertension in Latin American urban settings

1. Objectives/research questions/hypothesis:

The ***main objective*** of this proposal is to evaluate the effectiveness of an affordable and sustainable primary health care intervention to reduce blood pressure (BP) and prevent progression from pre-hypertensive status to hypertension in individuals at poor urban clinics in Guatemala. This study is part of a multicentric project conducted in Peru and Argentina.

Primary aim:

I. To determine the effects of mHealth strategies in a multi-country, one-year randomized control trial comparing intensive education for lifestyle modification to standard care in 30-60-year-old individuals with pre-hypertension.
Hypothesis IA Pre-hypertensive subjects who receive mHealth support for 12 months (intervention group) will have lower blood pressure compared to individuals who receive the usual primary health care (control group).
Hypothesis IB Pre-hypertensive subjects will maintain lower blood pressure six months after receiving mHealth support.

Secondary aims:

II. To establish healthy lifestyle changes (reduction of high sodium intake, increase potassium intake, regular physical activity, smoking cessation, stress reduction) and weight loss (body mass index) as a result of the intervention, and to determine their association with changes in blood pressure.
Hypothesis IIA Positive changes in knowledge and attitudes, adoption of healthy lifestyles, and weight loss will be greater among subjects in the intervention group at the end of the 12-month intervention and at 6-month follow-up.
Hypothesis IIB Greater adoption of healthy lifestyles and weight loss will be associated with lower blood pressure.

III. To explore the use /acceptability of cellular phones by patients and health personnel for health purposes and to develop and validate SMS texts and algorithms to guide telephone calls.

IV. To assess the feasibility, acceptability, and cost-effectiveness of the proposed intervention in the context of urban primary health care settings in the participating countries.

2. Background:

Age-adjusted cardiovascular death rates have risen significantly over the past few decades in low- and middle-income countries, which now carry about 80% of the burden of disease worldwide.[1] In Latin America, adult mortality due to CVD is estimated to increase 145% between 1990-2020.[2] Furthermore, CVD imposes a heavy toll on already over-burdened health care systems, and affects the economy and well-being of individuals, families, and the community at large. Pre-hypertensive individuals are at high risk of progressing to hypertension and developing CVD. Early interventions to increase the practice of healthy lifestyles in these high-risk individuals could reduce BP, decrease the rate of progression of BP to hypertensive levels, and even prevent hypertension entirely.[3][4] However, current primary care systems in developing countries lack preventive programs targeted at pre-hypertensive individuals. There is an urgent need to implement effective comprehensive prevention, screening, and management programs directed to pre-hypertensive subjects.

Mobile health or mHealth refers to the use of mobile telecommunication and multimedia technologies for health-related uses. mHealth is emerging as a useful tool to address several healthcare system constraints in the developing world, such as a limited health care workforce, limited financial resources, a high burden of disease combined with high population growth, and the challenge of extending health care to hard-to-reach populations.[5] mHealth is successfully being applied in developing countries for compliance with treatment of chronic infectious diseases such as TB and HIV/AIDS.[6][7] Studies in developed countries of behavior change using mHealth to promote weight loss, physical activity, and smoking cessation have shown positive promising results.[8][9] Currently no research have explored the efectivity of mHealth in developing country as a health promoter strategy. However, there is encouraging evidence of this type of interventions in Latin America. A Peruvian study reported that 70% of the diabetic patients indicated interest in participating in a program that uses cell phones to support treatment compliance regarding their disease. [10]

---

[1] Mathers CD, Lopez AD, Stein C, Fat DM, Rao C, Inoue M, Shibuya K, Tomijima N, Bernard C, Xu H. Deaths and disease burden by cause: global burden of disease estimates for 2001 by World Bank country groups. The World Health Organization (WHO), the World Bank, and the Fogarty International Center, US National Institutes of Health (NIH). DCPP Working Papers Series No. 18, Second Project on Disease Control Priorities in Developing Countries (DCPP). Bethesda, MD: WHO, 2005. Internet: http://www.dcp2.org/file/33/wp18.pdf (accessed 10 July 2010).

[2] Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation. 2001;104:2746-2753.

[3] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA. 2003;289:2560–2571.

[4] Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. BMJ. 1997;314:1666-1674.

[5] Mechael P, Batavia H, Kaonga N, Searle S, Kwan A, Goldberger A, Fu L, Ossman J. Barriers and gaps affecting mSalud in low and middle income countries: Policy white paper. Center for Global Health and Economic Development, Earth Institute, Columbia University, 2010. Internet: http://www.globalproblems-globalsolutions-files.org/pdfs/mSalud_Barriers_White_Paper.pdf (accessed 25 July 2010).

[6] Curioso WH, Kurth A. E. Access, use and perceptions regarding Internet, cell phones and PDAs as a means for health promotion for people living with HIV in Peru. BMC Med Inform Decis Mak. 2007;7:24.

[7] Blaya JA, Cohen T, Rodriguez P, Kim J, Fraser HS. "Personal digital assistants to collect tuberculosis bacteriology data in Peru reduce delays, errors, and workload, and are acceptable to users: cluster randomized controlled trial." International Journal of Infectious Diseases. 2009;13:410-418.

[8] Fjeldsoe BS, Marshall AL, Miller YD. Behavior change interventions delivered by mobile telephone short-message service. Am J Prev Med. 2009;(2):165-173

[9] Cole-Lewis H, Kershaw T. Text Messaging as a Tool for Behavior Change in Disease Prevention and Management. Epidemiol Rev. 2010;32:56-69.

[10] Curioso WH, Gozzer E, Valderrama M, et al. Uso y percepciones hacia las tecnologías de información y comunicación en pacientes con diabetes, en un hospital público del Perú. Rev. Peru Med Exp Salud Publica. 2009;26:161-167

3. Participantes:

Phase 1, the preparatory or formative phase: Eligible participants for focal group discussions (FGD) with community members are men and women, with and without high blood pressure, alphabets, who owns a personal cellular phone, and aged 30-60. Participants will be recruited in the health Clinic named Liga del Corazon located in Villa Nueva which will allow us to have access to a healthy and hypertensive population, with socio-demographic characteristics similar to our intervention population. All hypertensive subjects that participate in FGD will be taking anti-hypertensive medication as a proof of their diagnosis. Each FGD will consist of 5-8 members and will last approximately one and a half hour. Additionally, FGD will also be carried out with health personnel (one with medical staff and the other with non-medical staff). For this, health personnel with different range on ages, men and women, and that have direct contact with hypertensive and non-hypertensive patients (nurses, doctors, med students, laboratory personnel, etc.) will be recruited from primary health centers where the intervention will be completed (primary health clinics in Villa Nueva y Villa Canales). Each FGD will consist of 5-8 members. Health personnel that participate in the FGD will have their manager authorization prior their participation. No personal information will be collected from participants for the FGD.

Phase 2 or intervention: Eligible participants for pilot test and intervention are men and women, aged 30-60, pre-hypertensive (systolic BP values in the 120–139 mmHg range or diastolic BP in the 80-89 mmHg range), with confirmation of BP readings measured again by the study team, no current BP medication, and who own a personal cellular phone. Persons with previous diagnosis/treatment of hypertension or illiteracy will be excluded. Procedures to select only one participant per household will be pursued. An opportunistic recruitment will be performed in primary health clinics of poor urban settings of Guatemala City (Guatemala).

A pilot test with a convenient sample of 15 pre-hypertensive subjects will be performed. Subjects for the pilot test will be recruited in the health clinic of Santa Catarina Pinula to prevent any type of contamination of the intervention. For the intervention we plan to include 212 patients (106 patients per group, stratified by decade of age), assuming a 20% dropout rate. The primary health clinics where participants will be recruited are Villa Nueva y Villa Canales. This two health clinics were selected given the number of patients they received. This sample size will provide 90% power for a two-sided significance test with a Type I error of 0.05 to detect a mean difference of at least 5 mm Hg in systolic or diastolic BP between intervention and control groups. Such difference was chosen due to its clinical significance. Also, this sample size will allow for multivariable analysis, adjusting for up to 10 potential confounding factors.

Subjects participation in phase 1 of this study will be completely anonymous and no personal identifier will be collected. For Phase 2, the following identifiers will be collected: name, cell phone number, address, sex and age. This data will be kept in locked cabinets in the offices of the project staff to ensure the confidentiality of the collected information. Furthermore, electronic files will be protected with password.

4. Procedure:

This study consists of three phases. **Phase 1, the preparatory or formative phase**, focuses on the compilation, development, adaptation, and validation of culturally appropriate short messages and algorithms for lifestyle modification to be used in the intervention. IRB and other specific country

approvals, hiring and training staff, development of training manuals, and reproduction of educational materials will also take place in this phase. **Phase 2, the intervention phase**, includes a pilot-test text messages and algorithms; participant recruitment; collection of baseline data; implementation of a one-year, randomized control trial comparing intensive education for lifestyle modification to standard follow-up of individuals with pre-hypertension; and data collection during the 12-month intervention (months 6 and 12) and at 6-months post-intervention. **Phase 3, analysis of data**, also involves presentations of findings and write-up of results for publication (at both the scientific and policy levels).

Phase 1: Preparation and development of messages (6 months): To collect information for the development of educational messages and counseling tool four **focus group discussions** (FGD) with community members (with and without high blood pressure) and two FGD with health staff will be carried out. Community members will be recruited from primary health clinics while waiting to be attended by medical staff through oral invitation. Each FGD will consist of 5-8 members and will last approximately one and a half hour. As an incentive for participation a snack will be provided after the completion of the FGD. We will explore knowledge about hypertension risk factors, its consequences, and prevention methods and subjects' opinions about using cell phone calls and text messages to receive health advice. We will ask about their familiarity with cell phones, ability to receive calls and read text messages, and barriers that may hinder the intervention. FGDs with health personnel (one with medical staff and the other with non-medical staff) will be performed with staff that work in primary health clinics similar to the ones where the intervention will be carried out and will probe their experiences in giving health advice to pre-hypertensive patients, with attention to difficulties they have encountered while motivating patients to change health behaviors.

SMS messages will be developed using educational materials available in the participating countries, such as the Spanish version of the NHLBI manual for community health workers, *Your Heart, Your Life: A Lay Health Educator's Manual*, which has already been adapted and validated in Argentina and Guatemala, with NIH support. The research literature and educational resource websites will be searched for other validated tools. We will develop two SMS for each behavior change stage (5 per topic) and for each of the 6 topics (sodium intake, fruits and vegetables intake, weight control, physical activity, addictions and stress), up to 60 SMS in total. The content of text messages will be reviewed by experts in nutrition, physical activity, addictions (tobacco and alcohol), communication, and mental health from each country; they will be asked to complement or add to content as needed, and to identify the messages that they consider most important to communicate to pre-hypertensive patients during a year.

Algorithms used during phone calls will be based on the Transtheoretical Model (TTM) and the Health Belief Model (HBM), psychosocial theories widely used to explain individual behavior change. [11][12] The TTM affirms that behavioral change occurs in a series of five temporally ordered, discrete stages (precontemplation, contemplation, preparation, action, and maintenance).[13] The HBM identifies the primary factors that predict why people will take action to prevent illness; these include perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, and self-efficacy.[14] Callers (primary health care workers) will identify the relevant stage in the TTM continuum

[11] Hutchison AJ, Breckon JD, Johnston LH. Physical activity behavior change interventions based on the transtheoretical model: a systematic review. Health Educ Behav. 2009;36:829-845.
[12] Noia J, Prochaska JO. Dietary stages of change and decisional balance: a meta-analytic review. Am J Health Behav. 2010;34:618-632.
[13] Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol. 1983;51:390–395.
[14] Glanz K, Rimer B, Viswanath K. Health Behavior and Health Education. Theory, Research and Practice. Jossey – Bass. 4th Edition, 2008.

for each subject; depending on the stage, callers will introduce appropriate concepts proposed by the HBM to help subjects transition to the next stage. Motivational Interviewing (MI) will also be integrated into the algorithms. MI is a non-judgmental, guided, empathetic style of counseling that has been applied to a wide range of contexts to promote behavior change. Its goal is to increase intrinsic motivation through a flexible blend of informing, asking, and listening. The recommended techniques are expressed in the acronym GRACE: Generate a gap, Roll with resistance, Avoid arguments, Can do, and Express empathy.[15] Callers will use the GRACE techniques to increase patients' motivation and commitment and strengthen the relationship between callers and patients (see Table 1). Callers will record information received from and given to subjects on written forms. It will be necessary to develop an algorithm for each one of the 6 topics and an advice guide for each behavior change stage (5 stages). The algorithm content will be reviewed by nutrition, psychology, physical activity, addiction, and mental health experts in each country, whom will be asked to complement them as they consider necessary.

Table 1. Stages of change using the Health Belief Model and Motivational Interview approaches

TTM	Precontemplation	Contemplation	Preparation	Action	Maintenance
HBM	- Susceptibility - Severity	- Susceptibility - Severity - Benefits	- Barriers - Cues to action - Self-efficacy	- Cues to action - Self-efficacy	- Self - Efficacy
MI	- GRACE - Motivation	- GRACE - Motivation - Commitment	- GRACE - Commitment	- GRACE - Commitment	- GRACE - Commitment

Given that this is a multicenter study, text messaging development and algorithms preparation for phone calls, will be conducted simultaneously with the rest of the participating countries, aiming for similar final messages and algorithms, with the except of linguistic expression characteristic of each country. Before messages are pilot-tested, their wording will be reviewed and validated by a working group consisting of health personnel (physicians, nurses, social workers, and community health workers). Before launching the intervention, text messages will be subject to a second validation at the community level, to ensure that messages are understandable and acceptable to lay persons.

Phase 2: Pilot test, recruitment, intervention and baseline and outcome assessments (22 months)

Pilot test: To pilot-test text messages and algorithms, we will select a convenience sample of 15 pre-hypertensive patients from the health clinic at each site and invite them to participate in a one-month trial. During this trial participants will receive an initial 30-minute phone call from trained staff to identify their stages of the TTM and will receive a weekly text message (4 SMS in total). After that, a short telephone interview of approximate 30 minutes will explore the comprehension and acceptance of the information provided in the initial phone call and whether participants received all messages and their level of comprehension and acceptance of the four messages sent. Patients' opinions and recommendations about the interviewers will also be assessed.

[15] Sim M, Wain T, Khong E. Influencing behaviour change in general practice. Part 1 – Brief intervention and motivational interviewing. Australian Family Physician. 2009;38:885-888.

Recruitment and baseline assessment. Opportunistic recruitment will take place over about two to four months in selected clinics (Health clinic of Villa Nueva y Villa Canales) during normal operations and community health promotion activities organized by the staff (i.e health fairs). In preparation for the study, the research team will explain the study to the director and health staff; all nurses and physicians will be instructed to refer all subjects with BP in the pre-hypertensive range to the study physician, who will evaluate eligibility of participants and invite them to participate. Subject's participation will be entirely voluntary. Subjects detected with hypertension will be referred to regular medical care at the clinic. In addition to making the diagnosis of pre-hypertension and assessing inclusion/exclusion criteria, the study physician will carry out the consent process; perform anthropometry; and administer a questionnaire to assess dietary patterns related to sodium and potassium intake, physical activity, and inactivity behaviors, stress, and smoking and drinking habits.

Participants will be randomized to intervention or control group by the field director, using a computer-generated list with a 1:1 allocation. Randomization at the individual level leads to a more efficient design that improves power, and minimizes bias by controlling for any potential effects of clinic or country on the outcome measures. Given that the intervention uses cell phones, there is low risk for contamination of the control group by the intervention group.

The intervention will be conducted over 12 months. After baseline assessment, all subjects (intervention and control groups) will receive lifestyle modification counseling through a 30-minute talk given by trained staff (nurses/community health workers) and reinforced by printed educational materials. During the intervention period, participants in the intervention group will receive weekly educational SMS (48 in total, one per week) and monthly one-to-one phone calls (12 in total) by trained callers (nurses/community health workers). During the intervention, counseling will be given through phone calls and SMS of the following topics categories (diet, energy and addictions and stress) every 3 months (4 times during the 12-month intervention). Each category includes two topics:

Category	Topics
Diet	Sodium intake Fruit and vegetables intake
Energy	Weight control Physical activity
Addictions and stress	Addictions (tobacco, alcohol) Stress

After the baseline evaluation of each subject, an individual report will be generated, which will include the subject's information needed for the one-to-one phone calls (name, sex, age, body mass index, smoking and alcohol habits, stress score, etc) and an individualized order of the topics for the phone calls (i.e. weight control for overweight subjects). Every phone call will start with a questionnaire to explore the behavior change stage and self-efficacy of the subject. The questionnaire will be filled electronically by the caller, and a program will immediately generate the counsel items that should be used with each subject, according to his/her behavior change stage. After each one-to-one phone call, four SMS (one per week) will be sent to each subject, taking into account two issues: the topic counseled during the phone call and the behavior change stage in which the subject is for the particular topic. Each subject will receive up to 48 SMS per year (one weekly message).

Follow-up visits to the clinic for outcome assessments will take place at months 6 and 12, and six months after the end of the intervention. All participants (experimental and control group) will be

contacted by health personnel in charge of the study at least 4 times during the study time (one and half year). At each visit, performed at baseline, 6 and 12 months of intervention, and 6 months after the end of the intervention, a health professional will assess subject's blood pressure, weight, height, abdominal circumference, use of medication and behavioral risk factors (i.e smoking, exercise, diet, etc.). Subjects will be informed about their test results (BP and anthropometry) in each visit and those that progress to a hypertensive status will be referred to regular medical care at the clinic. Staff physicians involved in follow-up measures will be blinded to the treatment group. Upon completion of the study, we will offer educational SMS to the control group for six months.

***Intervention delivery methods*: SMS delivery**. We will use a free software program called FrontlineSMS that allows text messaging to large groups of people through a laptop plugged into a cell phone (http://www.frontlinesms.com/). The software stores all phone numbers, records all incoming and outgoing messages, and stores data in the laptop.

One-to-one phone calls. All calls will be made from a cellular phone number that will be displayed to subjects, along with the origin of the call, to facilitate identification of the intervention team and avoid scams. Calls will be made at a time previously arranged between caller and participant. An alternate telephone number will be requested from each participant in case a problem arises with the primary number (i.e., lost cell phone) and to reduce losses to follow-up. Each caller will make approximately three to four calls daily (Monday to Friday). During each call, the caller will fill out a form with the subject's ID, his/her answers to the questions posed, type of counseling given, and any comment/concerns that may arise.

***Outcome measures*: Blood pressure**, measured three times at three-minute intervals using a digital blood pressure monitor (OMRON, Model M5 or higher). The average of the second and the third measurements will be used to make the diagnosis. Pre-hypertension will be defined as systolic blood pressure between 120 and 139 mmHg and/or diastolic blood pressure between 80 and 89 mmHg.

Anthropometry (body weight, height, and waist circumference) will be measured in duplicate through standard techniques.[16] Weight will be measured using a calibrated digital scale with a precision of 100 g, height using a calibrated stadiometer to the nearest 0.1 cm, and waist circumference using an inextensible measuring tape. Body mass index (BMI) will be computed as weight (kg) divided by height squared (m^2). Overweight will be defined as a BMI between 25.0 and 29.9 and obesity as a BMI $\geq$ 30.0 kg/m^2.

Behavioral factors: **Dietary patterns** related to sodium and potassium intake will be assessed using an adapted short Food Frequency Questionnaire for foods high in sodium or potassium (to be validated during phase 1). **Physical activity** and inactivity will be assessed using the International Physical Activity Questionnaire[17], as well as other questions related to TV viewing and other sedentary activities. **Smoking status and alcohol consumption** will be ascertained using standardized questionnaires.[18] **Stress** will be measure using the Perceived Stress Scale (14-item version validated in Mexico), which assess the life events that are appraised as stressful.[19]

---

[16] Lohman T. Roche KA, Martorell R. eds. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics, 1991.
[17] Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381-1395.
[18] World Health Organization. *WHO STEPwise approach to Surveillance (STEPS). STEPS Manual*. Geneva: World Health Organization. At: http://www.who.int/chp/steps/manual/en/index.html.
[19] Ramirez, M. T. and Hernandez, R. L. Factor structure of the Perceived Stress Scale (PSS) in a sample from Mexico. Span J Psychol. 2007 May; 10(1):199-206.

Feasibility, acceptability, and cost-effectiveness*:* **Feasibility** will be assessed in terms of the expenses incurred, need for extra personnel, proportion of individuals in primary health care centers who are screened, infrastructure, and participant's retention rate. **Acceptability** will be assessed in terms of subjects' willingness to be screened, satisfaction, and adherence to management and follow-up protocols. Healthcare system resource use and costs over two years will be collected at the individual and site levels using microcosting techniques. A widely used and validated generic system of utility and preferences assessment (Euroqol EQ-5D) will be administered to study subjects at the initial and final visit. The primary outcome reported will be incremental **cost-effectiveness** of the intervention based on Quality-Adjusted Life Year (QALY), cost per mmHg of blood pressure difference between groups, and cost per diagnoses of hypertension prevented.

Health systems research*:* Given the diversity of health systems in the three participating countries, this project offers an unique opportunity to determine which aspects of the health systems in the intervention are shared between countries, as well as to highlight those issues that must be addressed in each country to facilitate successful implementation of a common intervention in each environment. We will collect systematic, comparable information on **adaptations** required to allow the use of mobile technology in each country ; **characteristics of the training** used in each country (e.g., profile of callers, selection process, who trained them, number of hours devoted to training, standardization procedures); **process followed at each site** to implement the intervention (e.g., timing of each activity, integration of SMS and one-to-one calls were embedded within routine care, average time spent on the phone calls, position of person in charge of calling, average number of calls required for each participant; integration of project activities into the daily routine of each participating center; usage of the clinic comparing intervention and the control groups, and **contextual variables** that might have influenced the outcomes.

The study team in each site will include a **Field Director** who will report directly to the PI in the country and who will be responsible for overseeing data collection, ensuring data quality, supervising and monitoring the callers, and managing any field related issue. Two **study physicians** will be responsible for detection, baseline assessment, and follow-up measures. Two **nurses or other health care providers** will be in charge of recruitment and one-to-one phone calls. Virtual sessions will we held monthly (via Elluminate and Skype) among all PIs and key personnel in each CoE to address coordination, training, and logistics issues. PIs well meet once each year.

Phase 3: Analysis, manuscript and presentation preparation (6 months): Analyses will be conducted using data from baseline and outcome assessment periods. This phase will also involve abstract submission, conference presentations, and manuscript preparation. Results from this study will be disseminated among the global scientific community interested in the topic as well as decision-makers in Latin America.

Data management and analysis**.** Data processing and storage will be centralized. A web-based platform for electronic data capture will be implemented based on the WHO platform OpenClinica (www.OpenClinica.org), which will be used to enter data from each site. Data managers at IECS will integrate all data received from each site. All data will be checked for validity and consistency. Data entry personnel will be trained and certified at all sites in the use of the system.

General characteristics of the population will be described using indicators of central tendency and dispersion. In the case of continuous variables, mean and median, range, standard deviation, and/or interquartile range will be calculated according to the distribution of each variable. In the case of categorical variables, absolute and relative frequencies will be calculated.

To assess the efficacy of the intervention, analysis will be performed on an intention-to-treat basis. For primary analysis and within each site, between-group differences in the change in blood pressure will be tested by analysis of variance. A multivariate analysis will be performed to adjust for potential confounders on blood pressure change from baseline using linear and robust regression techniques. Statistical analyses will be conducted with STATA (version 10.0).

The economic evaluation will use statistical analysis for multinational trials in order to address inter-country differences in population characteristics and treatment patterns (i.e., multivariate cost or outcome regressions to adjust for country effects, multilevel random effects model with shrinkage estimators, Bayesian modeling). Uncertainty will be addressed to evaluate the robustness of the results (probability sensitivity analysis to evaluate parameter uncertainty, imputation methods, long term extrapolation, and cost-effectiveness acceptability curves).

Health systems performance will be descriptive in nature and comparative analysis will highlight similarities and differences as well as practical lessons learned over the course of the project.

5. Information security and subjects privacy protection:

Research data will be obtained through FGD as well as through clinical measurements before, during and after intervention. We propose several mechanisms to ensure data integrity, which are summarized in a Data Safeguarding Plan. In brief, all study staff will be trained to promote standardized and objective collection and recording of participant information. Assessment instruments will be edited immediately after completion for legibility, consistency, and completeness. Data will be imported into a password-protected database, backed up through a secure off-site connection. We will set up several mechanisms to ensure the confidentiality of data collected from the participants. All paper files will be stored in locked file cabinets, and electronic files stored in password-protected files. Furthermore, both paper and electronic files will be identified only by a participant's ID number. Identifying information linking participants to their study ID number will be retained off site in a locked cabinet only accessible by the Principal/Co-Principal Investigators and project directors. Confidentiality policies and procedures will be reviewed with all new staff and reviewed annually with current staff.

To protect the confidentiality of participants we propose the following steps:

- No personal identifier will be collected from participants of FGD and all hard and electronic documents will be identified by assigning a unique ID number.
- We will retain the identifying information (name, phone number, sex, age) of participants of phase 2 that agree to be contacted during and 6 months after the end of the intervention. Once participant is enrolled in the study the site coordinator will assign an ID # to the participant. This number will be used to identify the case on all hard and electronic copy documents and will be part of the survey data that is entered. Neither names of respondents nor any other kind of identifier will appear on the questionnaires or in the questionnaire data files.
- All research data will be kept in a locked file and will be available only to research personnel involved directly in the study. The data will be identified only by an ID number. Participant's personal information, including name, telephone number and address; will be kept in a different place from the research data.
- All data collected will be transferred from the clinical sites to research headquarters for processing and later to INCAP to create a regional master database.

- There will be no electronic transmission and sharing of individually identifiable data. If for some reason this type of transmission becomes necessary, the data will be encrypted to prevent anyone without permission to access the data.
- Access to the data shall be limited to the minimum number of individuals necessary to achieve the approved purpose and to those individuals on a need-to-know basis only.
- We will store identifiable data in a locked cabinet when not in use.
- We will store original and derivative data files only on disks (e.g. servers, local hard disks) that are routinely backed up.
- We will pick up hardcopy printouts with respondent identifiable information from the printer as soon as they are printed.
- We will not transmit individually identifiable or deducible information derived from the data through unsecured telecommunications, including the Internet.
- We will not link records included in the data to any other identifiable source of information.
- We will delete or modify identifiers or data so that individual identifies can not be ascertained or deduced prior to the release of data outside the project team. Examples of such data elements include name, age, sex, phone number, etc.
- We will keep all hardcopy materials containing sensitive data in a locked file cabinet when not in use.
- When data are no longer needed, we will discard sensitive output in a shredder or sensitive-waste container.
- We will destroy all individual linkages to data one year after the completion of the project.
- We will report all serious violations of the Data Safeguarding Plan in writing to the Principal Investigator, with a copy to the Privacy Resource Office.

The PI for this project will have ultimate responsibility for data safeguarding, will assure that the proposed data protection procedures outlined here are adequately set in place in the field site, will overseeing the work of the field coordinator and field staff, making sure that pre-scheduled visits to the field take place as planned, will have the responsibility of training the field staff in data safeguarding techniques, as well as oversight of all staff who handle participant-identifying computer files, surveys, tracking forms, and other identifiable data. Every person involved in data collection or data handling will sign confidentiality agreements. Survey and clinical data will be strictly de-identified and will be electronically transmitted from the field to each country's main office location only by project staff. Data manager at IECS will integrate all information received from each site. Raw data and computer files will be kept at the research offices of project staff. All data that allow identification of study participants will be destroyed one month after the close of the project in each site using a paper shredder. Consent forms will be kept up to one year after the project is closed.

6. Recruitment process:

Phase 1 or formative, community members for the FGD will be recruited from a primary health clinic (Liga del Corazon located in Villa Nueva) through oral invitation while awaiting to be assisted by medical staff. FGDs with community members will be carried out with hypertensive men and women (one with 30-44 years old and the other with 45-60 years old subjects) and with non-hypertensive men and women (one with 30-44 years old and the other with 45-60 years old subjects). FGDs with health personnel (one with medical staff and the other with non-medical staff) will be conducted with staff that works in the primary health clinics of Villa Nueva y Villa Canales, where the intervention will place. Health staff will be recruited through oral invitation and will be scheduled for a specific date to conduct the FGD.

Pilot test subjects will be recruited from the primary health center located in Santa Catarina Pinula. This center is located in an area different to one used for the intervention in order to avoid any type of sample contamination. **Phase 2 or intervention** will be carried out in the primary health centers of Villa Nueva y Villa Canales. Opportunistic recruitment will take place over about two to four months during normal operations and community health promotion activities organized by the staff (i.e health fairs organized by health staff). All nurses and physicians will be instructed to refer all subjects with BP in the pre-hypertensive range to the study physician, who will evaluate eligibility of participants and invite them to participate.

7. Consent process and documentation:

Informed consent will be obtained from all participants. Participation on focus groups during Phase 1 will require only oral consent given that no personal information will be collected and participants will remain anonymous. Oral consent will describe the study purpose and procedures, clarifying and answering any question the participant might have. Only subjects that provide their oral consent will be asked to participate in the FGD.

A written consent form will be obtained from participants in the pilot test and intervention. A physician hired by the project will describe the details of the study to the potential participants, including the nature of the subject's involvement in the study, the possible risks and benefits of participation, and the individual's capacity to withdraw from the study at any time without consequence. Consent forms administered in Phase 2 for the intervention will specify the intention to follow-up participants for one year during the project (medical assessment at 6 and 12 month and phone contact through the use of weekly text messages and monthly phone calls), and six months later, when participants will contacted again for a another medical assessment. Participants will have the opportunity to review the consent form and to ask questions about the study, after which informed consent will be obtained and documented. Consent forms will be stored in a locked file cabinet. Each participant will be given a copy of the consent form to keep.

Additional questions or comments of participants during the study will be directed to the PI or Co-PI or their research staff listed in the last page of the written consent form.

8. Risks:

FGD does not pose a physical risk, although some people might feel uncomfortable in the presence of certain people. Participants are not obligated to respond to the questions if they desire to do it. There is always the possibility of confidentiality to be broken; all possible safeguard measurement will be taken to avoid this from happening (Section 5). Additionally, we will request to FGD participant to avoid sharing the information discussed during the session with other people.

The proposed study will apply a lifestyle education intervention, promoting better dietary practices, limiting salt (sodium) consumption, cessation of smoking, and regular practice of physical activity. There are no anticipated undesirable or adverse effects expected for this intervention. However, given that we will be screening individuals who may be unaware about their blood pressure status, and that it is common for hypertension to go unnoticed until a diagnosis is made, there is a chance that we may find individuals with high blood pressure. Individuals who have a high blood pressure reading will be informed about it, and will be immediately back referred to the primary health care clinic where they were contacted for a confirmation diagnosis and, if warranted, treatment.

There is a slight possibility that participants may experience psychological distress when receiving the news that they have a high blood pressure reading. We will take particular care in explaining that one high blood pressure reading does not make the diagnosis of hypertension, and will insist on the need for participants to seek a confirmation at the primary health care clinic.

A second source of psychological distress may emerge from the use of cell phones. In some of the field sites included, cell phones have been used for scams or to pose threats of a fake abduction of family members to demand ransom payment. We will get information related to this topic from the FGD, looking for methods to surpass this potential barrier.

A third source of psychological distress may come from the interviews, particularly when talking about stress-related events and hassles. We will take particular care in not raising any judgmental attitude during the interviews. Field staff will be instructed to allow interviewees not to answer any question that may seem uncomfortable, or to stop the interview if there is evidence of clear psychological distress.

Disclosure of personal mobile phone numbers to third parties and loss of confidentiality are potential adverse events, so we have set up several mechanisms to ensure the privacy and confidentiality of participants. The nature of any information that may need to be disclosed to protect the participants or others is included as part of the consent process.

9. Benefits:

No direct benefits exist from participating in the FGD in this study, but the possible satisfaction that can result from the contribution in the development of a program designed to improve the health and wellbeing of people with high blood pressure.

Participants may benefit directly from this trial, as the intervention is likely to improve their life style habits, their diet, and their health. We do not expect that participating in the proposed trial should involve increasing usual expenditures, as we will focus on improving lifestyle habits like the practice of regular exercise or the consumption of a healthy diet, within constrains of household budget.

The possible social effect of an intervention based on mHealth communication about how to practice a healthier life style is particularly appealing to further these activities in the field of public health in developing countries. This is true not only for Latin America, but also for other countries around the world that are undergoing the increased burden of cardiovascular diseases, which are currently affecting societies everywhere in the world at a faster rate than the health care service can attend.

10. Payment:

In previous research conducted in similar clinical settings in Guatemala it has not been a practice to offer compensation in cash to participants in field trials. In place of that, non-coercive token gifts, like a calendar for the house, may be used, as from previous experience we find that these are greatly appreciated, as well as being an incentive to sustain participation when a somewhat long trial is expected. Visits to the health center are scheduled according to the usual monitoring provided by the health system, they do not represent an additional burden of time that the study should compensate. Also, telephone calls will be scheduled whenever it is convenient for each subject, so that does not disrupt their work.

11. Plan to report unanticipated problems/adverse events:

No adverse effects are anticipated for this intervention. Any relevant information or unanticipated problem/adverse event that occurs during the study will be notified to the Ethics Institutional Committee through a written report within the 72 hrs of having knowledge of the occurrence of the event.

12. Other Ethic Committees:

The study in Guatemala will also be reviewed by the Ethics Committee of the U.S. RAND Corporation.

Institutional Review Board

Phase 2 or intervention phase protocol

Use of mobile technology to prevent progression of pre-hypertension in Latin American urban settings

Version. No. 4

Investigators from INCAP

Manuel Ramírez Zea, MD, PhD[1]
Paola Letona, MSc[1]
Julissa Salguero, MSc, RD[1]
Rebecca Kanter, PhD[1]

Investigators from other institutions

Adolfo Rubinstein, MD, MSc, PhD [2]
Jaime Miranda, MD, MSc, PhD [3]
Homero Martínez, MD, PhD [4]

[1]INCAP Comprehensive Center for the Prevention of Chronic Diseases (CIIPEC), Institute of Nutrition of Central America and Panama – INCAP, Guatemala, Guatemala
[2]Southern Cone American Center for Cardiovascular Health, Institute for Clinical Effectiveness and Health Policy – IECS, Buenos Aires, Argentina
[3]CRONICAS Center of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru
[4]RAND Corporation, Santa Monica, California, USA

1. Introduction:

Nearly half of the adult population in Latin American urban settings has abnormally high blood pressure. Although half of these subjects with high blood pressure are still in the pre-hypertensive stage, the rate of progression to hypertension is high (10-20% per year), according to studies done in other settings. The main objective of this proposal is to evaluate the effectiveness of an affordable and sustainable primary health care intervention to reduce blood pressure and prevent progression from pre-hypertensive status to hypertension in individuals at poor urban clinics in Argentina, Guatemala, and Peru. We will determine the effects of an intervention using mobile health (mHealth) technology, including short message services (SMS) and one-to-one telephone calls, to promote lifestyle modification focused on reducing blood pressure among participants. The intervention also aims to help participants become better informed, motivated, and encouraged to practice self-management of their own health; to improve patient satisfaction levels; provide tailored targeted interventions; and to improve patient-provider relationships.

The proposal is designed as a proof-of-concept intervention in three Latin American countries (Argentina, Guatemala and Peru) that encompass a wide range of environments and health care settings. The study has three phases: Phase 1 or *formative phase*, which is already completed and focused on the development and validation of culturally appropriate messages and algorithms for lifestyle modification; *an intervention phase or phase 2*, consisting of validation of text messages (SMS) developed in phase 1, a pilot test and a one-year randomized control trial to compare intensive education for lifestyle modification (intervention group) to standard care (control group); and a six-month post-intervention follow-up. And a last phase, *phase 3* for data analysis. We will also evaluate feasibility, acceptability, cost-effectiveness, and process implementation of the intervention.

This protocol includes only relevant information to Phase 2 or intervention phase of this study given that Phase 1 has already been reviewed and approved by the National Ethics Committee and Ethics Committee of INCAP. It was decided to obtain approval for this research protocol in phases because the information obtained in phase 1 provides valuable information for the development and design of instruments of the intervention phase.

2. Objectives/research question/hypotesis:

The ***main objective*** of this proposal is to evaluate the effectiveness of an affordable and sustainable primary health care intervention to reduce blood pressure (BP) and prevent progression from pre-hypertensive status to hypertension in individuals attending health centers in the department of Guatemala. This study is part of a multicenter project also taking place in Peru and Argentina.

Primary aim:

I. To determine the effects of mHealth strategies in a multi-country, one-year randomized control trial comparing intensive education for lifestyle modification to standard care in 30-60-year-old individuals with pre-hypertension.

Hypothesis IA Pre-hypertensive subjects who receive mHealth support for 12 months (intervention group) will have lower blood pressure compared to individuals who receive the usual primary health care (control group) after a year of intervention.

Hypothesis IB Pre-hypertensive subjects will maintain lower blood pressure six months after receiving mHealth support.

Secondary aims:

II. To establish healthy lifestyle changes (reduction of high sodium, fat and sugar intake, increase potassium intake and regular physical activity) as a result of the intervention, and to determine their association with changes in blood pressure.

Hypothesis IIA Positive changes in knowledge and attitudes, adoption of healthy lifestyles, and weight loss will be greater among subjects in the intervention group at the end of the 12-month intervention and at 6-month follow-up.

Hypothesis IIB Greater adoption of healthy lifestyles and weight loss will be associated with lower blood pressure.

III. To explore the use /acceptability of cellular phones by patients and health personnel for health purposes and to develop and validate SMS texts and algorithms to guide telephone calls.

IV. To assess the feasibility, acceptability, and cost-effectiveness of the proposed intervention in the context of urban primary health care settings in the participating countries.

3. Background:

Age-adjusted cardiovascular death rates have risen significantly over the past few decades in low- and middle-income countries, which now carry about 80% of the burden of disease worldwide.[1] In Latin America, adult mortality due to CVD is estimated to increase 145% between 1990-2020.[2] Furthermore, CVD imposes a heavy toll on already over-burdened health care systems, and affects the economy and well-being of individuals, families, and the community at large. Pre-hypertensive individuals are at high risk of progressing to hypertension and developing CVD. Early interventions to increase the practice of healthy lifestyles in these high-risk individuals could reduce BP, decrease the rate of progression of BP to hypertensive levels, and even prevent hypertension entirely.[3][4] However, current primary care systems in developing countries lack preventive programs targeted at pre-hypertensive individuals. There is an urgent need to implement effective comprehensive prevention, screening, and management programs directed to pre-hypertensive subjects.

Mobile health or mHealth refers to the use of mobile telecommunication and multimedia technologies for health-related uses. mHealth is emerging as a useful tool to address several healthcare system constraints in the developing world, such as a limited health care workforce, limited financial resources, a high burden of disease combined with high population growth, and the challenge of extending health care to hard-to-reach populations.[5] mHealth is successfully being applied in developing countries for compliance with treatment of chronic infectious diseases such as TB and HIV/AIDS.[6][7] Studies in developed countries of behavior

[1] Mathers CD, Lopez AD, Stein C, Fat DM, Rao C, Inoue M, Shibuya K, Tomijima N, Bernard C, Xu H. Deaths and disease burden by cause: global burden of disease estimates for 2001 by World Bank country groups. The World Health Organization (WHO), the World Bank, and the Fogarty International Center, US National Institutes of Health (NIH). DCPP Working Papers Series No. 18, Second Project on Disease Control Priorities in Developing Countries (DCPP). Bethesda, MD: WHO, 2005. Internet: http://www.dcp2.org/file/33/wp18.pdf (accessed 10 July 2010).

[2] Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation. 2001;104:2746-2753.

[3] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA. 2003;289:2560–2571.

[4] Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. BMJ. 1997;314:1666-1674.

[5] Mechael P, Batavia H, Kaonga N, Searle S, Kwan A, Goldberger A, Fu L, Ossman J. Barriers and gaps affecting mSalud in low and middle income countries: Policy white paper. Center for Global Health and Economic Development, Earth Institute, Columbia University, 2010. Internet: http://www.globalproblems-globalsolutions-files.org/pdfs/mSalud_Barriers_White_Paper.pdf (accessed 25 July 2010).

[6] Curioso WH, Kurth A. E. Access, use and perceptions regarding Internet, cell phones and PDAs as a means for health promotion for people living with HIV in Peru. BMC Med Inform Decis Mak. 2007;7:24.

change using mHealth to promote weight loss, physical activity, and smoking cessation have shown positive promising results.[8][9] Currently no research have explored the efectivity of mHealth in developing country as a health promoter strategy. However, there is encouraging evidence of this type of interventions in Latin America. A Peruvian study reported that 70% of the diabetic patients indicated interest in participating in a program that uses cell phones to support treatment compliance regarding their disease. [10]

4. Participants:

For text messages (SMS) validation will recruit men and women from the community, aged 30-60 years, literate, while waiting to be served by a clinician in different health centers of poor urban areas in Guatemala City. This activity will enroll a maximum of 40 subjects (10 men aged 30 to 44 years, 10 men aged 45 to 60 years, 10 women aged 30 to 44 years and 10 women aged 45 to 60 years) who will participate in individual interviews of 30 minutes to assess comprehension, appealing and usefulness of SMS that promote lifestyle modification focused on reducing blood pressure among participants.

Eligible participants for pilot test and intervention are men and women, aged 30-60, pre-hypertensive (systolic BP values in the 120–139 mmHg range or diastolic BP in the 80-89 mmHg range), with confirmation of BP readings measured again by the study team, no current BP medication, and who own a personal cellular phone. Persons with previous diagnosis/treatment of hypertension, diabetes, medical history of cardiovascular disease (stroke, coronary heart disease, peripheral vascular disease, renal disease) or illiteracy will be excluded. Procedures to select only one participant per household will be pursued. An opportunistic recruitment will be performed in health centers of poor urban areas in the department of Guatemala.

For the pilot test (1 month of duration) we will select and invite to participate 8 men and 8 women from a health center (Santa Catarina Pinula) similar to the health centers where the intervention will take place (Villa Nueva, Villa Canales y San Miguel Petapa). For the intervention we plan to include 212 patients (106 patients per group, stratified in two groups of age: 30-45 y and 46-60 years), assuming a 20% dropout rate. This sample size will provide 90% power for a two-sided significance test with a Type I error of 0.05 to detect a mean difference of at least 5 mm Hg in systolic or diastolic BP between intervention and control groups. Such difference was chosen due to its clinical significance. Also, this sample size will allow for multivariable analysis, adjusting for up to 10 potential confounding factors.

For subjects participating in phase 2 of this study, except those participating in individual interviews for SMS validation, the following identifiers will be collected: name, cell phone number, address, sex and age. This data will be kept in locked cabinets in the offices of the project staff to ensure the confidentiality of the collected information. No personal identifier will be collected for subjects participating in SMS validation.

---

[7] Blaya JA, Cohen T, Rodriguez P, Kim J, Fraser HS. "Personal digital assistants to collect tuberculosis bacteriology data in Peru reduce delays, errors, and workload, and are acceptable to users: cluster randomized controlled trial." International Journal of Infectious Diseases. 2009;13:410-418.

[8] Fjeldsoe BS, Marshall AL, Miller YD. Behavior change interventions delivered by mobile telephone short-message service. Am J Prev Med. 2009;(2):165-173

[9] Cole-Lewis H, Kershaw T. Text Messaging as a Tool for Behavior Change in Disease Prevention and Management. Epidemiol Rev. 2010;32:56-69.

[10] Curioso WH, Gozzer E, Valderrama M, et al. Uso y percepciones hacia las tecnologías de información y comunicación en pacientes con diabetes, en un hospital público del Perú. Rev. Peru Med Exp Salud Publica. 2009;26:161-167

5. Procedures:

This study consists of three phases. **Phase 1, the preparatory or formative phase**, which is already completed, reviewed and approved in Guatemala by the Ethics Committee of INCAP, and focused on the compilation, development and adaptation of culturally appropriate short messages and algorithms for lifestyle modification to be used in the intervention. **Phase 2, the intervention phase**, includes a series of individual interviews with community members for SMS and algorithm validation, a 1 month pilot-test; participant recruitment; collection of baseline data; implementation of a one-year, randomized control trial comparing intensive education for lifestyle modification to standard follow-up of individuals with pre-hypertension; and data collection during the 12-month intervention (months 6 and 12) and at 6-months post-intervention. **Phase 3, analysis of data**, also involves presentations of findings and write-up of results for publication (at both the scientific and policy levels). Following the details of phase 2 and 3 of this study given that phase 1 is already completed and approved.

Phase 2 or intervention phase:

Short text messages (SMS) validation: Individual interview will be carried out for validation of SMS created in phase 1 of this study (see SMS examples in appendix). Comprehension, appealing and usefulness of 48 SMS that promote lifestyle modification focused on reducing blood pressure (reducing sodium, fat and sugar intake, fruits and vegetable promotion and physical activity promotion) will be assessed through individual interviews. During each interview a series of SMS will be displayed and will use structured interview technique, using a short guide and open ended question, to assess content, clarity and acceptability of each message (see interview guide in appendix). Each interview will last a maximum of 30 minutes and the conversation will be recorded to avoid losing any important information.

Pilot test: a one-month pilot test of the intervention will be conducted in a health center (Health Center of Santa Catarina Pinula) similar to where the intervention will take place. We will invite 8 pre-hypertensive men and 8 pre-hypertensive women who will receive an initial 30-minute phone call from trained staff to identify their stages of change using the Transtheoretical Model (TTM, precontemplation, contemplation, preparation, action, and maintenance) for each of the topics to intervene. Given that 4 topics will be discussed in the intervention (sodium intake, fruits and vegetable intake, fat and sugar intake and physical activity) each one will be tested in 4 subjects during the pilot test. After the initial phone call, each subject will receive a weekly text message (4 SMS in total). After that, a short telephone interview will explore the comprehension and acceptance of the information provided in the initial phone call and whether participants received all messages and their level of comprehension and acceptance of the four messages sent. Patients' opinions and recommendations about the interviewers will also be assessed.

Intervention: this study will be conducted at health centers of poor urban settings of participating sites. In Guatemala, an opportunistic recruitment will take place over about two to four months in selected health clinics of poor urban areas (Health Center of Villa Nueva, Villa Canales y San Miguel Petapa) during normal operations and community health promotion activities organized by the staff (i.e. health fairs). All nurses and physicians at the primary health clinic will be instructed to refer all subjects with BP in the pre-hypertensive range to the study physician, who will evaluate eligibility of participants and invite them to participate. In addition to making the diagnosis of pre-hypertension and assessing inclusion/exclusion criteria, the study physician will carry out the consent process; perform anthropometry; and

administer a questionnaire to assess dietary patterns related to sodium and potassium intake, physical activity, and inactivity behaviors, stress, and smoking and drinking habits. After the initial assessment, each subject will be randomly assigned to control or experimental group using the minimization method for subject allocation.

All participants (experimental and control group) will be contacted by health personnel in charge of the study at least 4 times during the study time (one and half year). At each visit, performed at baseline, 6 and 12 months of intervention, and 6 months after the end of the intervention, a health professional will assess subject's blood pressure, weight, height, abdominal circumference, use of medication and behavioral risk factors (i.e. smoking, exercise, diet, etc.). Subjects will be informed about their test results (BP and anthropometry) in each visit and those that progress to a hypertensive status will be referred to regular medical care at the clinic. Staff physicians involved in follow-up measures will be blinded to the treatment group. Upon completion of the study, we will offer educational SMS to the control group for six months.

The intervention will be conducted over 12 months. After baseline assessment, all subjects (intervention and control groups) will receive lifestyle modification counseling through a 30-minute talk given by trained staff (nurses/community health workers) and reinforced by printed educational materials. To reduce the chances of lost of follow-up we will call participants before the random allocation to the control or experimental arm. This call will help to confirm that the phone number provided by the participant works (i.e. not out of service) and to confirm their willingness to participate in the study. This way we will only include those subjects who have more confidence to achieve the required follow-up of 18 months, where we expect a loss of follow-up lower to 20%. During the intervention period, participants in the intervention group will receive weekly educational SMS (48 in total, one per week) and monthly one-to-one phone calls (12 in total) by trained professional callers (nurses/dietitians/psychologist, etc.) about healthy lifestyles focused on reducing blood pressure. Motivational Interviewing (MI) will be used during phone calls. MI is a non-judgmental, guided, empathetic style of counseling that has been applied to a wide range of contexts to promote behavior change. Its goal is to increase intrinsic motivation through a flexible blend of informing, asking, and listening. During the intervention, counseling will be given through phone calls and SMS on the following topics:

- Diet (sodium, fruits and vegetables, fat and sugar intake)
- Physical Activity

After the baseline evaluation of each subject, an individual report will be generated containing the subject's information needed for the one-to-one phone calls (name, sex, age, body mass index, smoking and alcohol habits, stress score, physical activity level, sodium, fat, sugar, fruit and vegetable intake) and an individualized order of the topics for the phone calls. Every phone call will start with a questionnaire to explore the behavior change stage of the subject with respect to the topic to be discussed in the session and one-to-one telephone counseling will be provided considering the stage of change of the participant. After each one-to-one phone call, four SMS (one per week) will be sent to each subject to reinforce the counseling provided during the phone call. Each subject will receive up to 48 SMS per year (one weekly message).

Calls will be made at a time previously arranged between caller and participant. An alternate telephone number will be requested from each participant in case a problem arises with the primary number (i.e., lost cell phone) and to reduce losses to follow-up. Each caller will make approximately three to four calls daily (Monday to Friday). During each call, the

caller will fill out a form with the subject's ID, his/her answers to the questions posed, type of counseling given, commitments established during the call, and any comment/concerns that may arise. Telephone calls might be recorded for quality control purposes. Phone call tapes will only be used for this purpose and will be destroyed two years after the study is completed. Information provided during phone call will be confidential. To identify phone call recordings a code and no personal identification of participants will be used.

We will use a free software program called FrontlineSMS for SMS delivery that allows text messaging to large groups of people through a laptop plugged into a cell phone (http://www.frontlinesms.com/). The software stores all phone numbers, records all incoming and outgoing messages, and stores data in the laptop.

During the initial assessment at the primary health clinic, the study phone number, number used for SMS delivery and conduction of phone calls, will be saved at each participant cell phone as a strategy to facilitate participants identification of the study SMS and phone calls. This strategy is necessary to ensures participants will read the SMS and answer the incoming calls given the common practice to avoid answering phone calls from unknown numbers to avoid extortions and frauds.

The study team at each site will include a Field Director who will report directly to the PI in the country and who will be responsible for overseeing data collection, ensuring data quality, supervising and monitoring the callers, and managing any field related issue. Two study physicians will be responsible for detection, baseline assessment, and follow-up measures. Two nurses or other health care professionals will be in charge of recruitment, one-to-one phone calls and SMS delivery.

Phase 3 or Data Analysis:

Analyses, editing and result preparation will be conducted using data from baseline and outcome assessment periods. This phase will also involve abstract submission, conference presentations, and manuscript preparation. Results from this study will be disseminated among the global scientific community interested in the topic as well as decision-makers in Latin America.

Data processing and storage will be centralized. A web-based platform for electronic data capture will be implemented based on the WHO platform OpenClinica (www.OpenClinica.org), which will be used to enter data from each site. Data managers at IECS (Institute for Clinical Effectiveness and Health Policy – IECS, Buenos Aires, Argentina) will integrate all data received from each site. All data will be checked for validity and consistency. Data entry personnel will be trained and certified at all sites in the use of the system.

General characteristics of the population will be described using indicators of central tendency and dispersion. In the case of continuous variables, mean and median, range, standard deviation, and/or interquartile range will be calculated according to the distribution of each variable. In the case of categorical variables, absolute and relative frequencies will be calculated.

To assess the efficacy of the intervention, analysis will be performed on an intention-to-treat basis. For primary analysis and within each site, between-group differences in the change in blood pressure will be tested by analysis of variance. A multivariate analysis will be

performed to adjust for potential confounders on blood pressure change from baseline using linear and robust regression techniques. Statistical analyses will be conducted with STATA (version 10.0).

The economic evaluation will use statistical analysis for multinational trials in order to address inter-country differences in population characteristics and treatment patterns (i.e., multivariate cost or outcome regressions to adjust for country effects, multilevel random effects model with shrinkage estimators, Bayesian modeling). Uncertainty will be addressed to evaluate the robustness of the results (probability sensitivity analysis to evaluate parameter uncertainty, imputation methods, long term extrapolation, and cost-effectiveness acceptability curves).

Health systems performance will be descriptive in nature and comparative analysis will highlight similarities and differences as well as practical lessons learned over the course of the project.

6. Randomization:

Given the small sample size per site of this study (n=212 subjects per site, 106 subjects stratified in two groups of age: 30-45 y and 46-60 y) and to avoid significant group differences in key determinant factors the method of minimization for allocation of participants to groups will be used. This allocation uses an adjudication algorithm for participant's allocation among groups taking in consideration factors that might influences the results. This way, mentioned factors will be balanced among the control and experimental group to avoid bias in the results. The factors that will be considered for the minimization allocation in this study are: sex (masculine and feminine), age (30-45 years, 46-60 years) and stage of change of each subject (two levels: 1= willing to change, 2=not willing to change). On a weekly basis, the randomization coordinating center (IECS, Buenos Aires, Argentina) will perform group allocation for new participants for all sites. The algorithms will be applied using a software specially design for this purpose.

7. Outcome variables:

Blood pressure, measured three times at three-minute intervals using a digital blood pressure monitor (OMRON, Model 742-INT). The average of the second and the third measurements will be used to make the diagnosis. Pre-hypertension will be defined as systolic blood pressure between 120 and 139 mmHg and/or diastolic blood pressure between 80 and 89 mmHg.

Anthropometry (body weight, height, and waist circumference) will be measured in duplicate through standard techniques.[11] Weight will be measured using a calibrated digital scale with a precision of 100 g, height using a calibrated stadiometer to the nearest 0.1 cm, and waist circumference using an inextensible measuring tape. Body mass index (BMI) will be computed as weight (kg) divided by height squared (m^2). Overweight will be defined as a BMI between 25.0 and 29.9 and obesity as a BMI $\geq$ 30.0 kg/m^2.

Behavioral factors: Dietary patterns related to sodium, potassium, fat and sugar intake will be assessed using an adapted short Food Frequency Questionnaire for foods high in sodium, potassium, fat and sugar (see appendix). Physical activity and inactivity will be

[11] Lohman T. Roche KA, Martorell R. eds. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics, 1991.

assessed using the International Physical Activity Questionnaire[12], as well as other questions related to TV viewing and other sedentary activities (see appendix). Smoking status and alcohol consumption will be ascertained using standardized questionnaires[13](see appendix). Stress will be measure using the Perceived Stress Scale (14-item version Spanish version from Argentina), which assess the life events that are appraised as stressful[14] (see appendix).

Feasibility, acceptability, and cost-effectiveness: Feasibility will be assessed in terms of the expenses incurred, need for extra personnel, proportion of individuals in primary health care centers who are screened, infrastructure, and participant's retention rate. Acceptability will be assessed in terms of subjects' willingness to be screened, satisfaction, and adherence to management and follow-up protocols. Healthcare system resource use and costs over two years will be collected at the individual and site levels using microcosting techniques. A widely used and validated generic system of utility and preferences assessment (Euroqol EQ-5D) will be administered to study subjects at the initial and final visit (see appendix). The primary outcome reported will be incremental cost-effectiveness of the intervention based on Quality-Adjusted Life Year (QALY), cost per mmHg of blood pressure difference between groups, and cost per diagnoses of hypertension prevented.

Health systems research: Given the diversity of health systems in the three participating countries, this project offers an unique opportunity to determine which aspects of the health systems in the intervention are shared between countries, as well as to highlight those issues that must be addressed in each country to facilitate successful implementation of a common intervention in each environment. We will collect systematic, comparable information on adaptations required to allow the use of mobile technology in each country ; characteristics of the training used in each country (e.g., profile of callers, selection process, who trained them, number of hours devoted to training, standardization procedures); process followed at each site to implement the intervention (e.g., timing of each activity, integration of SMS and one-to-one calls were embedded within routine care, average time spent on the phone calls, position of person in charge of calling, average number of calls required for each participant; integration of project activities into the daily routine of each participating center; usage of the clinic comparing intervention and the control groups, and contextual variables that might have influenced the outcomes.

8. Information security and subjects privacy protection:

Research data will be obtained through clinical measurements before, during and after intervention. We propose several mechanisms to ensure data integrity, which are summarized in a Data Safeguarding Plan explained below.

In brief, all study staff will be trained to promote standardized and objective collection and recording of participant information. Assessment instruments will be edited immediately after completion for legibility, consistency, and completeness. Data will be imported into a password-protected database, backed up through a secure off-site connection. We will set up several mechanisms to ensure the confidentiality of data collected from the participants. All paper files will be stored in locked file cabinets, and electronic files stored in password-protected files. Furthermore, both paper and electronic files will be identified only by a

[12] Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35:1381-1395.
[13] World Health Organization. *WHO STEPwise approach to Surveillance (STEPS). STEPS Manual*. Geneva: World Health Organization. At: http://www.who.int/chp/steps/manual/en/index.html.
[14] Ramirez, M. T. and Hernandez, R. L. Factor structure of the Perceived Stress Scale (PSS) in a sample from Mexico. Span J Psychol. 2007 May; 10(1):199-206.

participant's ID number. Identifying information linking participants to their study ID number will be retained off site in a locked cabinet only accessible by the Principal/Co-Principal Investigators and project directors. Confidentiality policies and procedures will be reviewed with all new staff and reviewed annually with current staff.

To protect the confidentiality of participants we propose the following steps:

❖ We will retain the identifying information (name, phone number, sex, age) of participants of phase 2 that agree to be contacted during and 6 months after the end of the intervention. Once participant is enrolled in the study the site coordinator will assign an ID # to the participant. This number will be used to identify the case on all hard and electronic copy documents and will be part of the survey data that is entered. Neither names of respondents nor any other kind of identifier will appear on the questionnaires or in the questionnaire data files.

❖ All research data will be kept in a locked file and will be available only to research personnel involved directly in the study. The data will be identified only by an ID number. Participant's personal information, including name, telephone number and address; will be kept in a different place from the research data.

❖ All data collected will be transferred from the clinical sites to research headquarters for processing and later to INCAP to create a regional master database.

❖ There will be no electronic transmission and sharing of individually identifiable data. If for some reason this type of transmission becomes necessary, the data will be encrypted to prevent anyone without permission to access the data.

❖ Access to the data shall be limited to the minimum number of individuals necessary to achieve the approved purpose and to those individuals on a need-to-know basis only.

❖ We will store identifiable data in a locked cabinet when not in use.

❖ We will store original and derivative data files only on disks (e.g. servers, local hard disks) that are routinely backed up.

❖ We will pick up hardcopy printouts with respondent identifiable information from the printer as soon as they are printed.

❖ We will not transmit individually identifiable or deducible information derived from the data through unsecured telecommunications, including the Internet.

❖ Telephone call recordings will only be used for quality control purposes and will be destroyed two years after the study is completed. All information will be kept confidential and no personal identification will be used to identify phone call tapes.

❖ We will not link records included in the data to any other identifiable source of information.

❖ We will delete or modify identifiers or data so that individual identifies can not be ascertained or deduced prior to the release of data outside the project team. Examples of such data elements include name, age, sex, phone number, etc.

❖ We will keep all hardcopy materials containing sensitive data in a locked file cabinet when not in use.

❖ When data are no longer needed, we will discard sensitive output in a shredder or sensitive-waste container.

❖ We will destroy all individual linkages to data one year after the completion of the project.

❖ We will report all serious violations of the Data Safeguarding Plan in writing to the Principal Investigator, with a copy to the Privacy Resource Office.

The PI for this project will have ultimate responsibility for data safeguarding, will assure that the proposed data protection procedures outlined here are adequately set in place in the field site, will overseeing the work of the field coordinator and field staff, making sure that pre-

scheduled visits to the field take place as planned, will have the responsibility of training the field staff in data safeguarding techniques, as well as oversight of all staff who handle participant-identifying computer files, surveys, tracking forms, and other identifiable data. Every person involved in data collection or data handling will sign confidentiality agreements. Survey and clinical data will be strictly de-identified and will be electronically transmitted from the field to each country's main office location only by project staff. Data manager at IECS will integrate all information received from each site. Raw data and computer files will be kept at the research offices of project staff. All data that allow identification of study participants will be destroyed one month after the close of the project in each site using a paper shredder. Consent forms will be kept up to one year after the project is closed.

9. Recruitment process:

Community members that participate in individual interviews for SMS validation will be recruited in different health centers of poor urban settings of Guatemala City while waiting to be served by a clinician. A maximum of 40 subjects for this activity will be recruited.

Pilot test will be conducted with a convenient sample of 16 pre-hypertensive subjects and will be carried out in a health center similar to where the intervention will be conducted. For the intervention, an opportunist sample of 212 pre-hypertensive subjects will be recruited over a period of two to four months in selected primary health clinics during normal operations and community health promotion activities organized by the staff (i.e health fairs organized by health staff).

In preparation for the study, the research team will explain the study to the director and health staff; all nurses and physicians will be instructed to refer all subjects with BP in the pre-hypertensive range to the study physician, who will evaluate eligibility of participants and invite them to participate. Subject's participation will be entirely voluntary. Subjects detected with hypertension will be referred to regular medical care at the clinic. In addition to making the diagnosis of pre-hypertension and assessing inclusion/exclusion criteria, the study physician will carry out the consent process; perform anthropometry; and administer a questionnaire to assess dietary patterns related to sodium and potassium intake, physical activity, inactivity behaviors, stress, and smoking and drinking habits. After the initial assessment, each subject will be randomly assigned to control or experimental group using the minimization method for subject allocation.

10.Consent process and documentation:

An oral informed consent (see appendix) will be obtained from subjects participating in individual interviews and a written informed consent (see appendix) for subjects participating in the pilot test and intervention. During the consent process we will describe the study purpose and procedures, clarifying and answering any question the participant might have.

Oral informed consent for individual interviews will be obtained by a field worker in charge of recruitment process prior to the beginning of the interview. Interviews will be completely anonymous and no identifiers will be collected.

A written consent form will be obtained from participants in the pilot test and intervention. A physician hired by the project will describe the details of the study to the potential participants, including the nature of the subject's involvement in the study, the possible risks and benefits of participation, and the individual's capacity to withdraw from the study at any time without consequence. The consent form for the pilot text will specify the

intention to follow participants for a month. Consent forms administered for the intervention will specify the intention to follow-up participants for one year during the project (medical assessment at 6 and 12 month and phone contact through the use of weekly text messages and monthly phone calls), and six months later, when participants will contacted again for a another medical assessment. Participants will have the opportunity to review the consent form and to ask questions about the study, after which informed consent will be obtained and documented. Consent forms will be stored in a locked file cabinet. Each participant will be given a copy of the consent form to keep.

Additional questions or comments of participants during the study will be directed to the PI or Co-PI or their research staff listed in the last page of the written consent form.

11.Risk:

Individual interviews with community members do not pose a physical risk, although some people might feel uncomfortable with some questions. Participants are not obligated to respond to the questions if they desire not to do so. There is always the possibility of confidentiality to be broken; to avoid this, interviews will be completely anonymous and no identifiers will be collected from participants.

The proposed pilot test and intervention will apply a lifestyle education intervention, promoting better dietary practices, limiting salt (sodium), fat and sugar consumption, promotion of fruits and vegetable intake, and regular practice of physical activity. There are no anticipated undesirable or adverse effects expected for this intervention. However, given that we will be screening individuals who may be unaware about their blood pressure status, and that it is common for hypertension to go unnoticed until a diagnosis is made, there is a chance that we may find individuals with high blood pressure. Individuals who have a high blood pressure reading will be informed about it, and will be immediately back referred to the primary health care clinic where they were contacted for a confirmation diagnosis and, if warranted, treatment. Given that phone calls might be recorded for quality control purposes there is a slight possibility that confidentiality might be broken. To avoid this, codes and no personal identifiers will be used to identify phone call tapes. Also, the recordings will only be used for the purpose of quality control and will be destroyed two years after the study ends. All call information will be kept confidential.

There is a slight possibility that participants may experience psychological distress when receiving the news that they have a high blood pressure reading. We will take particular care in explaining that one high blood pressure reading does not make the diagnosis of hypertension, and will insist on the need for participants to seek a confirmation at the primary health care clinic.

A second source of psychological distress may emerge from the use of cell phones. In some of the field sites included, cell phones have been used for scams or to pose threats of a fake abduction of family members to demand ransom payment. To avoid this, all SMS and telephone calls related to the study will be properly identified with the number and name of the program or any other way that has been agreed with the participant.

Disclosure of personal mobile phone numbers to third parties and loss of confidentiality are potential adverse events, so we have set up several mechanisms to ensure the privacy and confidentiality of participants. The nature of any information that may need to be disclosed to protect the participants or others is included as part of the consent process.

12.Benefits:

No direct benefits exist from participating in the individual interviews of this study, but the possible satisfaction that can result from the contribution in the development of a program designed to improve the health and wellbeing of people with high blood pressure. Participants may benefit directly from this trial, as the intervention is likely to improve their life style habits, their diet, and their health.

We do not expect that participating in the proposed trial should involve increasing usual expenditures, as we will focus on improving lifestyle habits like the practice of regular exercise or the consumption of a healthy diet, within constrains of household budget.

The possible social effect of an intervention based on mHealth communication about how to practice a healthier life style is particularly appealing to further these activities in the field of public health in developing countries. This is true not only for Latin America, but also for other countries around the world that are undergoing the increased burden of cardiovascular diseases, which are currently affecting societies everywhere in the world at a faster rate than the health care service can attend.

13.Payment:

In previous research conducted in similar clinical settings it has not been a practice to offer compensation in cash to participants in field trials. In place of that, non-coercive token gifts, like a calendar for the house, may be used, as from previous experience we find that these are greatly appreciated, as well as being an incentive to sustain participation when a somewhat long trial is expected. Visits to the health center are scheduled according to the usual monitoring provided by the health system, they do not represent an additional burden of time that the study should compensate. Also, telephone calls will be scheduled whenever it is convenient for each subject, so that does not disrupt their work.

14.Plan to report unanticipated problems/adverse events:

No adverse effects are anticipated for this intervention. Any relevant information or unanticipated problem/adverse event that occurs during the study will be notified to the Ethics Institutional Committee through a written report within the 72 hrs of having knowledge of the occurrence of the event.

15.Other Ethics Committees:

This protocol in Guatemala will also be reviewed by the National Ethics Committee and Ethics Committee of the U.S. RAND Corporation.