ACCOMPANEERS STUDY DETAILED PROTOCOL

Study Protocol and Statistical Analysis Plan

Impact of Community Health Workers on Adherence to Therapy for Non-Communicable Chronic Disease in Chiapas, Mexico

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I. BACKGROUND AND SIGNIFICANCE

a. Historical Background

Community health workers (CHWs), a term broadly applied to trained lay health workers, play an important role in health systems worldwide. CHWs have been viewed as an essential component of primary level health care since the Alma Ata declaration of 1978[1], and have played a crucial role in combatting the HIV epidemic. Randomized trials have documented the efficacy of CHWs in improving adherence to therapy among HIV patients in the developing world[2], as well as disease-specific outcomes such as CD4 count and HIV viral load.[3-4]

Non-communicable diseases (NCDs) such as diabetes and hypertension are the leading cause of death worldwide, and disproportionately affect the developing world. According to the WHO, 63% of deaths worldwide in 2008 were due to NCDs, but 80% of NCD deaths occurred in the developing world. The United Nations views renewed focus on NCD control as a public health necessity.[5]

Depression is a leading cause of disability worldwide, and at least half of affected people do not receive effective treatment for depression.[6] Even when effective pharmacologic treatment is delivered, between one and two thirds of patients do not respond to the first antidepressant prescribed, and high relapse and recurrence rates are common.[7, 8]

CHWs offer a potentially lower-cost, culturally sensitive option to help care for patients with NCDs and depression in the developing world.[9]

b. Previous pre-clinical or clinical studies leading up to, and supporting the proposed research

CHWs have been shown to be associated with improvement in a number of disease metrics in patients with NCDs in the US, particularly among medically underserved populations. Observational data support improvements in patient knowledge, positive lifestyle changes, self-care, healthcare utilization, adherence to therapy and hemoglobin A1c among patients with diabetes and hypertension in the US.[10-12] Recent years have seen several domestic randomized controlled trials showing clinically and statistically significant improvement in A1c, healthcare utilization and medication adherence among diabetic patients,[11-14] as well as improvements in cholesterol, blood pressure and A1c in patients attending urban health centers.[15]

CHWs have also been shown to be effective in the treatment of depression in rural settings, particularly when trained in basic psychoeducation.[16 - 18] Their impact on medication adherence is less well established.

Data from the developing world are lacking. To our knowledge, this study will be the first systematic assessment of the impact of CHWs vs. routine care for patients with NCDs in the developing world. As such, it will directly address World Health Organization and United Nations calls for advancement of care of patients with NCDs in the developing world.

Compañeros en Salud (CES) is an affiliate project of Partners in Health, an international non-governmental organization with extensive experience in the use of CHW interventions to help patients to manage chronic disease.[19] Since February 2012, CES has been working in the Sierra Madre region of rural Chiapas, Mexico, in partnership with the local Ministry of Health, to rehabilitate and staff existing government primary care clinics. Each community's clinic is staffed by one CES project physician year-round. CES activities span the range of primary care, but the focus of the project is in the prevention, detection, diagnosis and management of NCDs. At the time of study initiation, CES operated in six rural communities; they expanded to four additional communities after the study began (two were added August 2014, and two more February 2015). Routine care for NCDs is based on national guidelines and consists of monthly in-clinic visits by primary care physicians. Routine care of major depressive disorder includes monthly in-clinic visits, psychoeducation, and daily medications when indicated.

CES has conducted several community outreach programs to identify community members living with NCDs, including an active case finding program consisting of door to door visits at every home in the catchment area of CES clinics. Screening activities include a risk factor questionnaire for diabetes and hypertension as well as in-home blood pressure screening and referral for blood glucose and blood pressure screening when indicated. They also include screening for depression, and referral for diagnosis in the clinic when indicated. This approach allows diagnosis of chronic disease in an environment in which patients traditionally seek care only for acute illness, and has allowed for diagnosis of a majority of patients living in project communities with hypertension or diabetes. These patients have been started on treatment and are being followed by CES physicians in the clinics in a monthly basis.

In July 2012, CES piloted a CHW program utilizing CHWs locally called "Acompañantes" (aka. Accompaneers, in English) in one of its project communities to augment care of patients with NCDs. Accompaneers are lay health workers, nominated by their communities, who bridge the gap between project clinics and patients, improving patients' understanding of NCDs, their treatments, and the importance of adherence to therapy. CES physicians offer participation in the Accompaneer program to patients diagnosed with hypertension, diabetes, and depression, in addition to other diseases requiring daily therapy. Accompaneers conduct regular home visits to educate patients, support medication adherence, identify barriers to accessing care, and ensure the timely supply of medications. They are trained using a series of standardized educational sessions, and CES supervisors provide oversight. To date, over 80% of patients with NCDs have opted for the support of an Accompaneer. In our pilot community, the CES physician report fewer treatment interruptions, greater disease literacy and improved clinic attendance in the Accompaneer pilot community.

Plans for Expansion: Based on the observed impact of the pilot phase of the Accompaneer program on improving the adherence to treatment for patients with chronic diseases and its correlation with clinical outcomes, CES plans to expand the program to all project villages. **We will take advantage of this pre-planned programmatic expansion to prospectively evaluate this intervention, which is planned to continue indefinitely, regardless of study findings.**

c. Rationale behind the proposed research, and potential benefits to patients and/or society

Unique Opportunity for Evaluation: CHW interventions have been an important part of many health care systems throughout the world. Unfortunately, they are often implemented without systematic evaluation of their impact. CES's programmatic plan for phased expansion of the Accompaneers program offers a natural opportunity to study the intervention in a prospective, systematic manner.

Potential Programmatic Benefits for CES: This study will help to evaluate the impact of a CHW intervention to improve the care for patients with NCDs and depression. Support for a CHW intervention would serve as a cornerstone for programmatic expansion within CES to improve the quality of care of patients with NCDs within the program catchment area. Furthermore, this study may provide evidence for cross-site implementation of similar programs within the broader network of Partners in Health, as well as in other areas of Mexico.

Potential Implications for Health Systems: If effective, CHW interventions would offer a means of low-cost, culturally sensitive, integrated care for patients with NCDs in the developing world.

II. SPECIFIC AIMS

a. Specify objectives and hypotheses to be tested in the research project

Aim 1. Assess the impact of a CHW intervention on changes in adherence to medications for patients with diabetes, hypertension and depression

Aim 2. Assess the impact of a CHW intervention on scheduled clinic visit attendance for patients with diabetes, hypertension and depression
Aim 3a. Assess the impact of a CHW intervention on changes in Hb A1c in diabetic patients
Aim 3b. Assess the impact of a CHW intervention on changes in systolic and diastolic blood pressure in patients with hypertension
Aim 3c. Assess the impact of a CHW intervention on changes in Patient Health Questionnaire-9 (PHQ-9)[20] scores among patients with depression
Aim 4. Assess health beliefs, literacy, and satisfaction with medical care among patients participating in a CHW intervention.

III. SUBJECT SELECTION

a. Inclusion/exclusion criteria

Inclusion criteria:

- Formal diagnosis of Type II Diabetes Mellitus, Stage I or II Hypertension, Major Depressive Disorder, or two or more of the aforementioned diagnoses. Diabetes is defined as a fasting plasma glucose ≥ 126. Hypertension is defined as systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90, observed on at least two separate occasions. Major Depressive Disorder is defined as a diagnosis of Major Depressive Disorder by the clinic physician, following DSM-V diagnostic criteria and scoring a PHQ-9 ≥10.
- Daily medications prescribed for control of patient's condition at at least one point in time
- Residence within the study catchment area
- Age greater than or equal to 18

Exclusion criteria:

- Known or suspected secondary hypertension. Includes all patients with hypertension due to a comorbid medical condition, such as hyperthyroidism, pheochromocytoma, renal artery stenosis, etc.
- Known or suspected Type 1 diabetes
- Pregnancy-induced hypertension
- Gestational diabetes
- Chronic use of glucocorticoids
- Normal bereavement or complicated grief
- Depressive disorder due to another medical condition
- Substance or medication induced depressive disorder
- Past or present history of mania or hypomania
- Schizophrenia or schizoaffective disorder
- Adjustment disorder with depressed mood

b. Source of subjects and recruitment methods

CES physicians maintain a registry of all known patients living with hypertension, diabetes and depression in their communities, as diagnosed by active case finding or through regular clinic visits. All patients meeting inclusion criteria will be prescreened by CES physicians, who are not study investigators, to ask if study staff may approach them for enrollment. Study enrollment will be independent of, and will not affect eligibility for, enrollment in the Acompaneers program.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment, including procedures for patient registration and/or randomization

Study enrollment will be conducted by trained study staff that are independent of the patient's health care providers and clinical care. In the communities in which we plan to conduct the study, the usual way of approaching someone for a meeting is to approach them at home. Furthermore, it is important to avoid conflating study activities with clinical care, given the limited experience with research studies in these communities. Study staff will therefore go to patients homes to enroll them in the study. Patients declining enrollment in the study will still be eligible for participation in the Accompaneers program when it is introduced to their community.

Safety of study staff will be ensured by working in teams with established itineraries for home visits. In cases of medical emergency, CES physicians operate fully stocked primary care clinics in all project villages, a satellite phone is available in communities for study volunteers, and project cars are available for emergency transportation.

b. Procedures for obtaining informed consent (including timing of consent process)

Informed consent will be obtained during a pre-defined study enrollment period. Study staff will approach eligible patients at home or in clinic to solicit consent using a standardized consent form (see attached Study Consent form). Verbal consent will be obtained and documented.

c. Treatment assignment, and randomization (if applicable)

Please see Schema (attached) for visual explanation of study procedures.

Randomization: All communities will receive CHW accompaniment programs, but will be randomized at the community level in the order of program rollout. At present, CES only has the capacity to roll the Accompaneers program out to new project villages once every three months. Accordingly, prior to study commencement the order of rollout of the Accompaneers program to each of the project villages (Communities "A" through "D") will be assigned at random. Following data collection in the first four study communities, the remaining four communities will be randomized (Communities "E" through "G").

Patient enrollment in Accompaneers program (specific to enrollment in program, not in research study): When the Accompaneers program is introduced to a community, all eligible patients will be offered the option of participation in the program. Those accepting participation will be introduced to an Accompaneer in the clinic, and program home visits will commence in the week following enrollment.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured (e.g. laboratory tests, x-rays and other testing)

The study will not involve additional clinical study visits. Home visits will be conducted for questionnaire administration, conducted by trained study staff who are not CHWs or CES physicians. These visits will also include point-of-care testing of hemoglobin A1c and blood pressure, which will be recorded on study forms, after which samples will be destroyed; no samples will be sent to laboratories for testing (see section Ve.) Home visits with patients with depression will include questionnaires on adherence only.

b. Drugs to be used (dose, method, schedule of administration, dose modifications, toxicities), include Toxicity Grading Scale (if applicable)

The study will not involve additions or changes to therapeutic medication regimens.

c. Devices to be used

The study will not involve additional medical devices.

d. Procedures / surgical interventions, etc.

The study will not involve additional procedures or surgical interventions.

e. Data to be collected and when the data is to be collected

Data collection will be conducted by trained study staff that are independent of the patient's health care providers and clinical care. An enrollment questionnaire will be administered at the time of study enrollment (see attached Enrollment Form). Questionnaires related to medication adherence will be administered by study staff prior to study initiation and every three months thereafter until study completion (see attached Adherence Questionnaire, and translated version). Study staff will also conduct assessment of hemoglobin A1c, and systolic and diastolic blood pressure during these visits. Hemoglobin A1c will be assessed using fingerprick point-of-care technology, which gives an immediate result in the patient's presence. Data will be immediately transferred to data collection forms, then deleted from data collection devices and collection strips used to collect blood will be discarded in the patient's presence. No blood samples will be stored or transported as part of this study. These assessments and interviews will take place in the participant's home or the clinic, according to the participant's preference.

The study will involve collection of data from the medical record, which will be achieved by the use of unique patient identifiers linking to medical record numbers. Chart reviews will be conducted by study staff, and will be limited to those data specified in data collection forms (see attached Medical Records Form). No additional data will be collected from the medical record.

Questionnaires related to health beliefs, health literacy, and satisfaction with medical care will be conducted at baseline and at three month intervals after study initiation among selected patients by study staff (see attached Qualitative Supplement, and translated version).

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study (e.g. data collection sheets).

All study data will be collected using data collection sheets (see attached, per above).

Primary study outcomes:

- Self-report of medication adherence, as derived from study questionnaires adapted from validated measures.[21-23]

Secondary study outcomes:

- Proportion of scheduled monthly chronic disease appointments attended in preceding three months.
- Systolic and diastolic blood pressure (hypertension patients)
- Hemoglobin A1c (diabetes patients)
- PHQ-9 scores (patients with depression)
- Qualitative assessments of patients' health beliefs, health literacy, and satisfaction with medical care

b. Study endpoints

Study timeframe: The study, including the enrollment period and baseline data collection, will run for approximately 44 months in total. Baseline data collection and participant enrollment will occur concurrently prior to study initiation; this period is anticipated to take approximately one month. The study will then run for the subsequent continuous 21 months in the original communities, then conclude. Upon completion of data collection in the original four communities ("A" – "D"), baseline data collection and participant enrollment in the four remaining communities ("E" – "H") will commence; this period is expected to take approximately one month. Thereafter, the study will run in these communities for the subsequent continuous 21 months.

c. Statistical methods

Patients will be categorized as having adequate adherence based on pre-determined cutoff points from the standardized assessments. Hypertensive patients with a systolic blood pressure of <140 mmHg and a diastolic blood pressure of <90 mmHg (<130 mmHg and <80 mmHg, respectively, in patients with comorbid diabetes), and diabetic patients with a hemoglobin A1c of less than 7.0% will be defined as having achieved disease control. The stepped wedge crossover study design[24] allows for pre- and post-intervention comparisons with the added benefit of accounting for time-related bias. Due to the small number of communities and expected variation in the number of participants per community, we will use random-effects generalized estimating equations with "sandwich" variance estimates to conduct individual-level analyses adjusted for clustering at the community and individual levels.

d. Power analysis (e.g. sample size, evaluable subjects, etc)

With an average of 32 patients per community with diabetes or hypertension across the eight study communities, an 80% participation rate, and eight data collection periods per community (baseline, 3 months, 6 months, 9 months, and 12 months), we will have greater than 80% power to detect a 40% change in adherence, assuming a 50% of individuals meet the definition of good adherence prior to the intervention. These estimates are intentionally conservative, with lower baseline rates of adherence, greater improvements in adherence, and greater program participation observed in our pilot community.

With 50 patients with depression total in communities "E"-"H", utilizing a paired t-test, and anticipating a baseline adherence of 50%, we will have 90% power to detect a 40% improvement in adherence, an effect similar to that seen in the preliminary results from communities "A" – "D".

VII. RISKS AND DISCOMFORTS

a. Complications of surgical and non-surgical procedures, etc.

Participation in this study will not expose participants to procedural complications.

b. Drug side effects and toxicities

Participation in this study will not increase participants' exposure to drug side effects or toxicities.

c. Device complications / malfunctions

Participation in this study will not expose participants to device complications or malfunctions.

d. Psychosocial (non-medical) risks

There is a small risk that participation in this study may increase the risk that patients' diagnoses are known by the community at large due to study staff visits. Independent of study participation, we anticipate that most participants will consent to frequent home visits by Accompaneers, whose job within the community will be well-known, so we believe our study reflects a minimal increased risk in this regard. The study is independent of CES program activities, and patients may decline study participation and still have an Accompaneer. Study staff will be instructed not to identify the purpose of their visits to community members outside the group of study participants.

e. Radiation Risks (statement provided by the Radiation Safety Committee)

Participation in this study will not expose patients to risks of radiation.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

There are no potential benefits to participating individuals from participation in the study. CHW accompaniment via the Accompaneers program may be beneficial to participants' disease understanding and control, but will be offered regardless of study participation.

b. Potential benefits to society (e.g. increased understanding of disease process, etc.)

This study will answer crucial questions about the role of CHW interventions in the management of NCDs. It will have implications for health systems and may lead to more cost-effective, culturally relevant primary care.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

A full Data Management Plan is included in the attached files. Study data will be collected and stored by trained study personnel. Patient medical records will be stored in public clinics as per national guidelines. De-identified data will be made available upon request to any interested third party after publication of study results.

b. Safety monitoring (e.g. Data Safety Monitoring Board, etc.)

No additional safety monitoring is planned during this study.

c. Outcomes monitoring

No additional outcomes monitoring is planned during the study

d. Adverse event reporting guidelines

Because this study does not involve changes in therapeutic medical regimens for participants, it is not anticipated that adverse medical events will occur. Study staff noting hypertensive urgency or emergency will refer patients to CES physicians for treatment. Challenges or complaints from participants regarding study data collection or study staff will be reported to study leadership, and patients will be offered the option of withdrawal from the study. Challenges or complaints in the CHW accompaniment program will be reported to the program leadership, including supervisors of the CHW program, independent of study investigators.

X. REFERENCES

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XI. ATTACHMENTS

- Study consent
- Schema
- Enrollment Form (English and Spanish)
- Adherence questionnaire (English and Spanish)
- Medical record form
- Qualitative supplement (English and Spanish)
- Data Management Plan