Study Title: Implementing HEARTS in Guatemala

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Implementing integrated hypertension and diabetes management using the World Health Organization's HEARTS model: Protocol for a pilot feasibility study in the Guatemalan national primary care system

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Competing interests: MDH has pending patents for heart failure polypills. George Health Enterprises Pty Ltd (GH) and its subsidiary, George Medicines Pty Ltd, have received investment funds to develop fixed-dose combination products, including combinations of blood pressure-lowering drugs. GH is the social enterprise arm of The George Institute for Global Health.

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1. PROTOCOL SUMMARY

Background: The HEARTS Technical Package was developed by the World Health Organization to address the implementation gap of cardiometabolic care in low- and middle-income countries. Guatemala is a middle-income country that is currently implementing HEARTS. National authorities are interested in exploring how hypertension and diabetes management can be integrated in HEARTS implementation. The objective of this study is to conduct a feasibility and acceptability pilot trial of integrated hypertension and diabetes management based on HEARTS in the publicly funded primary care system in Guatemala.

Methods: A single-arm pilot trial for 6 months will be carried out in 11 Ministry of Health primary care facilities starting in August 2023. A planned sample of 100 adult patients diagnosed with diabetes (n=45), hypertension (n=45), or both (n=10) will be enrolled. The intervention will consist of HEARTS-aligned components: Training health workers on **H**ealthy-lifestyle counseling and **E**vidence-based treatment protocols; strengthening **A**ccess to medications and diagnostics; training on **R**isk-based cardiovascular disease management; **T**eam-based care and task sharing; and **S**ystems monitoring and feedback, including implementation of a facility-based electronic monitoring tool at the individual level. Co-primary outcomes of feasibility and acceptability will be assessed using quantitative data, qualitative data, and mixed methods. Secondary outcomes include clinical effectiveness (glycemic and blood pressure control), key implementation outcomes (adoption, fidelity, usability, and sustainability), and patient-related outcome measures (diabetes distress, disability, and treatment burden). Using an implementation mapping approach, a Technical Advisory Committee will develop implementation strategies for subsequent scale-up planning.

Discussion: This trial will produce evidence on implementing HEARTS-aligned hypertension and diabetes care in the MOH primary care system in Guatemala. Results also may inform HEARTS implementation efforts in other low- and middle-income countries.

2. ABBREVIATIONS

AEs	Adverse events
AIM	Acceptability of Intervention Measure
APEASE	Acceptability, feasibility, effectiveness, cost-effectiveness, side effects or unintended consequences, safety, and equity
CSAT	Clinical Sustainability Assessment Tool
DBP	Diastolic blood pressure
DDS	Diabetes Distress Scale
DHIS2	District Health Information System 2
FBG	Fasting blood glucose
FIM	Feasibility of Intervention Measure
HbA1c	Hemoglobin A1c
HEARTS	Healthy lifestyle counseling, Evidence-based protocols, Access to medicines, Risk-based management, Team care and task sharing, and Systems monitoring (World Health Organization's model for the primary care management of cardiometabolic diseases)
INCAP	Institute of Nutrition of Central America and Panama
IRB	Institutional review board
LMICs	Low- and middle-income countries
MOH	Ministry of Health
MULTIPleS	Multimorbidity Illness Perceptions Scale
NIH	National Institutes of Health
ORIO	Other reportable information or occurrence
PAHO	Pan American Health Organization
PI	Principal investigator
PROEDUSA	Department of Health Training and Education
PSAT	Program Sustainability Assessment Tool
REDCap	Research Electronic Data Capture
SBP	Systolic blood pressure
SIAS	Comprehensive Health Care System
SIGSA	Health Management Information System
TAC	Technical Advisory Committee
TICD	Tailored Implementation in Chronic Diseases
WHO	World Health Organization

3. BACKGROUND AND RATIONALE

Approximately 80% of the global burden of hypertension and diabetes occurs in low- and middle-income countries (LMICs).[1] Widespread adoption of evidence-based treatment of these diseases in high-income countries contributes to markedly better outcomes than in LMICs, where adoption is often limited.[2-6] To address this implementation gap, the World Health Organization (WHO) developed the HEARTS Technical Package.[7] HEARTS is an integrated model for the primary care management of cardiometabolic diseases. The model has six components: Healthy lifestyle counseling, Evidence-based protocols, Access to medicines, Risk-based management, Team care and task sharing, and Systems monitoring. The HEARTS components align with successful multicomponent interventions such as the U.S. Kaiser Permanente hypertension program.[8] HEARTS was designed to be a flexible platform to improve cardiometabolic care within national primary care systems.

Through its "Hearts in the Americas" initiative, the Pan American Health Organization (PAHO) has spearheaded efforts to implement HEARTS in national health systems throughout the Americas region.[9] HEARTS implementation projects to date have focused on hypertension as it the highest-burden cardiovascular disease risk factor.[10] To further its impact, HEARTS can be expanded to integrate management of other cardiometabolic diseases such as diabetes.[11] The HEARTS-D module primarily focuses on clinical diabetes recommendations. Given the diversity of health systems where HEARTS is implemented, there is thus a need for generalizable evidence on how integrated hypertension and diabetes care can be achieved, scaled, and sustained.[11]

Guatemala is a middle-income country with the highest burden of cardiometabolic diseases in Central America.[12] An estimated 32.2%[4] and 13.1%[13] of Guatemalan adults have hypertension and diabetes, respectively, and the two diseases account for one-quarter of national deaths.[12] This project builds on prior hypertension control projects in Guatemala by study investigators and collaborators in the Ministry of Health (MOH) and PAHO. From 2017-2022, study team members implemented a HEARTS-aligned multicomponent hypertension project across MOH primary care facilities in 5 of the country's 22 departments.[14-16] In 2021, study team members initiated a HEARTS pilot in 6 MOH primary care facilities. Finally, in November 2022, HEARTS was officially launched by the MOH and PAHO.[17] While HEARTS in Guatemala initially focuses on hypertension, national authorities are interested to exploring how diabetes can be integrated into ongoing implementation efforts. This trial will pilot the Integrated Hypertension and Diabetes Primary Care Model based on HEARTS in the publicly funded primary care system in Guatemala.

4. STUDY OBJECTIVE

The primary objective of this study is to test the feasibility and acceptability of an integrated model hypertension and diabetes management based on HEARTS in the publicly funded primary care system in Guatemala. The terms *feasibility* can refer to different concepts and domains in pilot studies.[18] In this protocol, we use the term specifically in reference to implementation outcomes. Secondary objectives of this study are to rehearse study procedures and to engage with key stakeholders to develop implementation strategies for a subsequent scale-up project.

5. METHODS

This protocol follows SPIRIT guidelines for clinical trial protocols.[19] Guidance on reporting non-randomized pilot studies, conducting pilot implementation studies and applying mixed methods to pilot studies also were applied as appropriate.[20,21]

5.1. Study design

A single-arm pilot trial over 6 months duration will be carried out in 11 Ministry of Health (MOH)-led primary care facilities. A single-arm design was chosen as most appropriate to evaluate feasibility and acceptability and to align with recommendations for pilot projects in the HEARTS Implementation Guide.[22]

5.2. Study setting

5.2.1. Participating health facilities

This study will be carried out in 11 MOH primary care facilities in two health districts (**Figure 1**). The two health districts were selected in consultation with the MOH and PAHO. Each health district includes one second-level primary health facility (health center) and referring first-level primary health facilities (health posts). A breakdown of these primary care facilities is shown in **Table 1**. Both health districts were sites where the study team previously implemented HEARTS-aligned hypertension control projects. The two health districts were purposefully selected to represent important areas of diversity in Guatemala across location and ethnicity. Neither health district was part of the initial wave of HEARTS implementation in Guatemala (see 5.1: Context of HEARTS implementation in Guatemala). It was also important that each site had motivated MOH leadership.[22] The selected health district in Sololá (San Pablo La Laguna) is located in the Central Highlands and has a primarily indigenous Maya population. The selected health district in Chiquimula (Esquipulas) is located in Eastern Guatemala and has a primarily non-Indigenous population. Both health districts have poverty rates of 60-70%[23] with large rural populations.[24]

Figure 1: Map of study setting

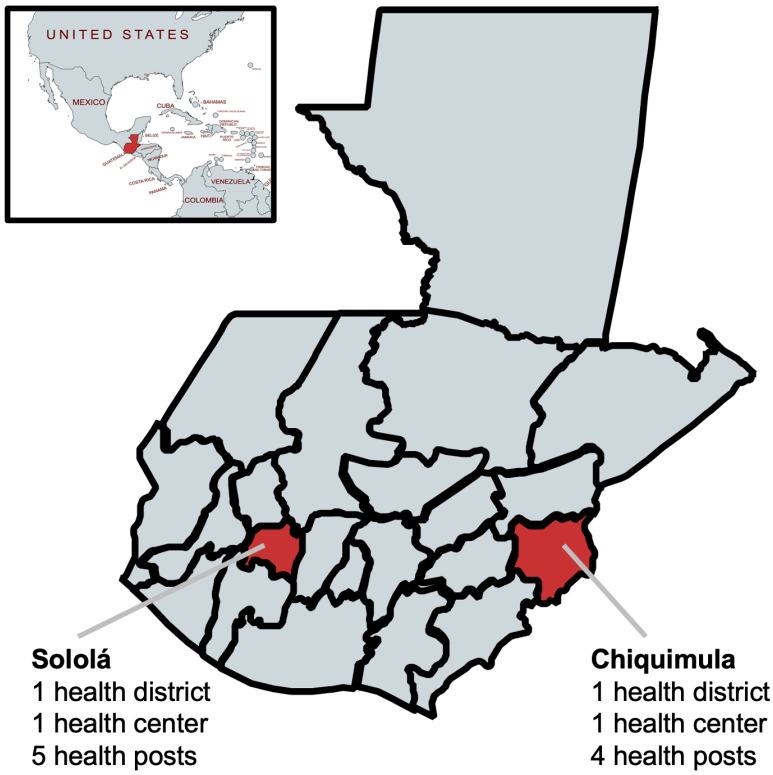


Table 1: MOH primary care sites for implementation

Department (health area)	Health district	Health centers, n	Health posts, n	Location	Population of health district	Ethnic group
Sololá	San Pablo La Laguna	1	5	Central Highlands	88,623	94.5% Maya Indigenous
Chiquimula	Esquipulas	1	4	Eastern Guatemala	55,556	96.3% non-Indigenous
Total		**2**	**9**			

5.2.2. Study context

Most poor patients with hypertension and diabetes in Guatemala depend on the Ministry of Health-led system for health care. The MOH system is a national, publicly funded system consisting of multiple levels.[25] The first two levels are the primary care levels where this project will be conducted. Primary care in the MOH system is coordinated by the Comprehensive Health Care System (*Sistema Integral de Atención en Salud* [SIAS]), which is a department in the MOH responsible for health service delivery. The National Program for the Prevention of Chronic Non-Communicable Diseases and Cancer coordinates hypertension and diabetes policies in the MOH.[26]

The first level of the MOH system are health posts. Health posts are located in rural villages, are typically open during business hours on weekdays, and are staffed by 1-2 auxiliary nurses. Auxiliary nurses are full-time MOH employees and have similar training to

nursing assistants in the U.S. health care system. Their scope of practice includes a wide range of basic preventative and curative primary care services, though auxiliary nurses typically do not provide pharmacological management of non-communicable diseases such as diabetes or hypertension.

- The second level of the MOH system are health centers. Health centers are located in urban or semi-urban areas in mid-sized towns, are open 24/7 for emergencies, and are staffed by professional nurses, general physicians, physicians-in-training, or a combination thereof. Professional nurses have similar training to registered nurses in the U.S. health care system, and their scope of practice encompasses that of auxiliary nurses with additional responsibility for more complex patient management . Health centers manage uncomplicated diabetes or hypertension cases. Available resources typically include oral medications and tools for measuring blood glucose and blood pressure.

- The third level of the MOH system are hospitals. Hospitals are located in regional capital cities and in Guatemala City, are open 24/7, and have additional staffing above health centers, including physician specialists. MOH hospitals have both inpatient and outpatient services for complex patients. Patients needing insulin therapy, acute inpatient care, or specialist management of diabetes or hypertension complications are referred to this level of care per the MOH protocols describe below.

Clinical guidelines. The MOH regularly releases clinical guidelines for primary care clinicians in Guatemala. The most recent hypertension and diabetes guidelines were released in 2018, were updated in 2023,[27] and are generally consistent with international guidelines.[28] The main challenge relating to clinical guidelines in Guatemala is the need for investments to support guideline implementation, including staffing, training and supervision, and equipping primary care facilities with clinical resources.

Clinical data systems. At present, there is no standardized paper or electronic patient medical record in the MOH-led health system. As a result, there is difficulty tracking individual patients over time or between health system levels. There is also no official diabetes or hypertension registry. The MOH has an electronic tool, the Health Management Information System, that is primarily used to monitor patient volume and to manage staffing needs (*Sistema de Información Gerencial de Salud* [SIGSA]). However, the SIGSA system is not designed to capture longitudinal patient data, and thus clinicians cannot use the system to provide clinical care with information from prior encounters with the health system.

Availability and cost of medications and diagnostics. Guatemalan laws guarantee that health care is free of charge at MOH health facilities.[25] The MOH thus is responsible for ensuring the availability of quality medications and supplies relating to hypertension and diabetes. At the primary care level, the most commonly available medications for hypertension are hydrochlorothiazide, enalapril, and losartan; the most commonly available medications for diabetes are metformin and glimepiride. Tests such as hemoglobin A1c (HbA1c), creatinine, or cholesterol are not available at MOH-led primary care facilities, though patients sometimes present results obtained at private laboratory facilities. Stockouts of medications and diagnostics commonly occur.[29]

Context of HEARTS implementation in Guatemala. In November 2022, with support from PAHO, the Guatemalan MOH committed to participate in the “Hearts in the Americas” initiative.[17] The MOH plans a stepped implementation of HEARTS across the country. The first 36 health districts across 6 of 22 departments in the country were enrolled in late 2022 and

2023. (“Departments” are first-level political subdivisions in Guatemala and are analogous to U.S. states.; each department has an corresponding administrative “health area” in the MOH system.) As noted above, neither of the sites in this pilot were included in the initial wave of HEARTS implementation in Guatemala. The MOH has committed resources to HEARTS, in particular to improve access to medications and supplies. To date, HEARTS implementation in Guatemala has focused only on hypertension management at MOH health centers. Diabetes management is not currently part of the MOH’s HEARTS strategy.

5.3. Participant eligibility criteria

5.3.1. Patient participants

Inclusion criteria: All non-pregnant adults aged ≥18 years with diagnoses of type 2 diabetes, hypertension, or both conditions who present for routine care at participating MOH primary health facilities between over a 6-month period will be included (“patient participants”).

Both previously diagnosed and newly diagnosed patients will be eligible. Previously diagnosed patients will be identified by MOH primary care clinicians who take medical histories as part of routine care. Newly diagnosed patients will be identified by MOH primary care clinicians who apply hypertension and diabetes diagnostic criteria from national guidelines.[27,28]

- Diabetes diagnostic criteria for newly diagnosed patients: fasting glucose ≥126 md/dl, two-hour post-prandial glucose ≥200 md/dl, HbA1c ≥6.5%.
- Hypertension diagnostic criteria for newly diagnosed patients: include systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg. A new hypertension diagnosis must be based on the average of at least two measurements performed on two separate occasions.

Exclusion criteria: Participants with confirmed or suspected type 1 diabetes or who are pregnant will be excluded, as these patients are not managed at MOH health centers or health posts. Participants with a prior history of cardiovascular disease will not be excluded.

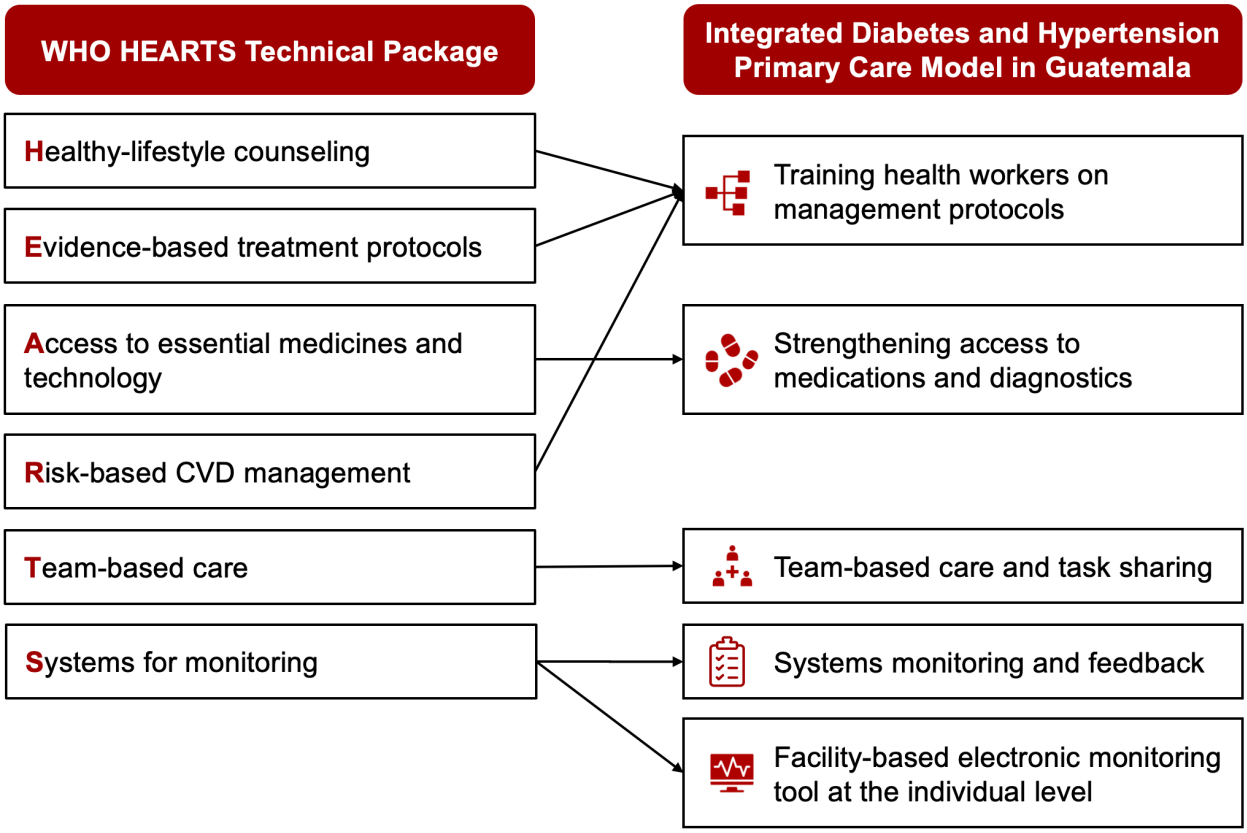
5.3.2. Other participants

All MOH staff (physicians, nurses, auxiliary nurses) and stakeholders on the Technical Advisory Committee will be eligible for participation in the implementation assessment of the pilot (“MOH participants”). Details on the Technical Advisory Committee members are provided in 7.3.5.

5.4. Intervention

We designed the intervention (“Integrated Hypertension and Diabetes Primary Care Model” [*Modelo Integral de Hipertensión y Diabetes en la Atención Primaria*]) based the study team’s prior implementation research projects[14-16,30,31] and discussions with the MOH and PAHO. Each of the components previously has been tested in the study team’s prior hypertension projects, but the focus on integrated diabetes management is novel in this project. The intervention consists of five HEARTS-aligned components (**Figure 2**). These components together comprise the evidence-based clinical intervention we seek to implement, which we define as: “pharmacological and non-pharmacological treatment of hyperglycemia and hypertension in primary care.”

Figure 2: Intervention components



5.4.1. Training health workers on hypertension and diabetes management

This component includes training on healthy-lifestyle counseling, evidence-based treatment protocols, and risk-based cardiovascular disease management. Training workshops will be conducted for first and second level health workers, including auxiliary nurses, professional nurses, and physicians, to provide instruction in standardized screening, diagnostic, and treatment protocols for hypertension and diabetes in MOH guidelines.[27,28] Initial workshops will be divided into two blocks, each lasting two days, in the first month of the project. A refresher training session also will be provided in the fourth month of the project. Sessions will be delivered separately at each health district's office headquarters. The sessions will be provided separately The training will adapt a curriculum previously used in the study team's HEARTS-aligned projects and approved by the Department of Health Training and Education (*Departamento de Promoción y Educación en Salud* [PROEDUSA]), which is the unit in the MOH/SIAS charged with continuing medical education. Workshop content will include the following topics: an introduction to hypertension and diabetes, diagnostic criteria, use of stepped treatment protocols, treatment targets, medication side effects, counseling to promote lifestyle changes, motivational interviewing, team-based care, capture and use of electronic patient data, and other topics. Participants will knowledge assessments before and after training workshops. Of note, MOH treatment targets for diabetes are fasting glucose 70-115 mg/dL, post-prandial glucose 70-160 mg/dl, or HbA1c <7.0; MOH treatment targets for hypertension are <130/80 mm/Hg.[28,32,33]

5.4.2. Team-based care and task sharing

To implement hypertension and diabetes care in health posts, we will implement a team-based, task-sharing care model between auxiliary nurses staffing health posts and prescribing clinicians (i.e., physicians or professional nurses) at health centers. This intervention component was implemented in the study team's prior hypertension project and has been approved by the MOH.[15] Physicians or professional nurses will make initial patient treatment plans. Auxiliary nurses working in health posts will implement treatment plans by dispensing medications, monitoring glycemic or blood pressure control, and titrating medications under physician supervision. Monthly care coordination meetings will be held in-person or remotely at least once per month to review patient registries and make recommendations for patients whose hypertension or diabetes is not adequately controlled according to MOH guidelines.[27,28] In our prior projects, monthly meetings have been difficult to operationalize.[34] Therefore, we may suggest an alternative approach in which auxiliary nurses at health posts communicate with physicians at health centers in real-time via text messages or phone calls to make treatment changes for uncontrolled patients.

5.4.3. Strengthening access to medications and diagnostics

We have extensive experience collaborating with the MOH to improve medication procurement and logistics at MOH health centers and health posts. In the study team's hypertension project in five departments, nearly 100% availability of key medications was achieved in MOH facilities over a course of three years. In the current project, we will expand the scope to improve access to diagnostics and medications for diabetes at participating MOH primary care facilities. We will coordinate with and train MOH staff on topics that include forecasting demand, seasonal budgeting, storage, shipping, and other topics. The focus will be on a small set of MOH priority medications and diagnostics. Drugs include antihypertensive medications (i.e., hydrochlorothiazide, enalapril, losartan) and oral hypoglycemic agents (i.e., metformin and glimepiride). Diagnostics including blood pressure cuffs and monitors, glucometers, lancets, and glucose strips. As noted in 5.1.2, all medications and diagnostics are provided freely to patients in the MOH. The implementation of a facility-based electronic monitoring tool, described below, also functions to improve available of medications and diagnostics by providing enhanced data to monitor supply and demand at primary care facilities.

5.4.4. Facility-based electronic monitoring tool at the individual level

As described above, there is currently no electronic or paper medical record system in primary care in the MOH system. There is also no registry of patients with diabetes or hypertension, and thus, it is not possible to monitor patient or population data on diabetes or hypertension awareness, treatment, and control in the MOH. To address this gap, the study team previously has collaborated with the MOH to pilot the District Health Information System 2 (DHIS2) in health centers and health posts. DHIS2 is an open-source, facility-based electronic monitoring tool that can monitor key indicators at the individual and aggregate levels.[35] We will implement the DHIS2 system including both hypertension and diabetes modules in MOH primary care facilities. Registries of patients with hypertension and diabetes will be constructed at each MOH facilities. The project will provide hardware (e.g., tablets or desktop computers), internet connectivity, technical support, and training and supervision of MOH staff. The DHIS2 system will be hosted on a centralized server, allowing for trained health workers to enter data and monitor patient data in real time. In the WHO classification system for digital health

interventions, this intervention component is a healthcare provider intervention focusing on client health records.[36]

5.4.5. Systems monitoring and feedback of key indicators

HEARTS requires the use of routine administrative clinical data to monitor key indicators and to iteratively improve the quality of hypertension and diabetes care.[37] Each month, we will present aggregate reports of key indicators using data drawn from DHIS2 to MOH stakeholders at the health district (i.e., municipal) and health area (i.e., departmental) levels. The key indicators will be the same as the HEARTS-aligned secondary outcomes described below. We will use a suite of DHIS2 visualization tools built by PAHO, including maps, graphs, and dashboards. In the WHO classification system for digital health interventions, this intervention component is a health system manager intervention focusing on facility management.[36] Facility-level monitoring using DHIS2 will be complemented by ongoing health worker training (5.3.1) and site supervision visits (5.3.4).

6. OUTCOMES

6.1. Primary outcomes

Primary outcomes will be feasibility and acceptability as defined in the Implementation Outcomes Framework (**Table 2**).[38] These outcomes will be assessed using quantitative data, qualitative data, and mixed methods (integrated qualitative and quantitative data). Given the study team's prior experience with HEARTS-aligned projects, the focus of the feasibility and acceptability assessments will be on integrating diabetes into the HEARTS model.

Feasibility is the extent to which a new intervention can be successfully carried out in an organization.[38] Among MOH participants, feasibility will be assessed through the four-item Feasibility of Intervention Measure (FIM) questionnaire[39] and semi-structured interviews. Among patient participants, feasibility will be assessed using enrollment data.

Acceptability is the stakeholders' perception that a new intervention is agreeable or satisfactory.[38] Among MOH participants, acceptability will be assessed using the Acceptability of Intervention Measure (AIM) questionnaire[39] and semi-structured interviews. Among patient participants, acceptability will be assessed using follow-up visit data and semi-structured interviews.

Table 2: Measures of feasibility and acceptability and their benchmarks

Measure	Minimum benchmark
Feasibility	
Feasibility questionnaire (FIM) among MOH participants	Median ≥3.5[a]
Reasons for perceptions of feasibility/infeasibility	N/A
Number of patient participants with diabetes enrolled per health district[b]	25
Number of patient participants with hypertension enrolled per health district[b]	25
Acceptability	
Acceptability questionnaire (AIM) among MOH participants	Median ≥3.5[a]

Table 2: Measures of feasibility and acceptability and their benchmarks

Measure	Minimum benchmark
Proportion of patient participants with subsequent follow-up visit within 3 months (among those enrolled with ≥3 months remaining in pilot)	75%
Reasons for perceptions of acceptability/infeasibility among patient and MOH participants	N/A
Reasons for dropouts among patient participants	N/A

Primary outcomes in this pilot study are feasibility and acceptability as defined in the Implementation Outcomes Framework. [a]The FIM and AIM scales range from 1 to 5 with higher values implying greater feasibility or acceptability, respectively; scores are averaged within each participant. [b]Enrollment is defined by a patient having at least one clinic visit entered in the DHIS2 or equivalent longitudinal medical record system; a given patient may have both diabetes and hypertension and thus count toward each benchmark. Abbreviations: AIM: Acceptability of Intervention Measure; FIM: Feasibility of Intervention Measure; MOH: Ministry of Health.

6.2. Secondary outcomes

Secondary outcomes include clinical outcomes, implementation outcomes, and patient-related outcome measures (**Table 3**).

Clinical effectiveness outcomes are based on recommended HEARTS monitoring indicators.[37,40] Clinical outcomes are assessed to provide pilot data to key MOH stakeholders and to rehearse study procedures rather than to evaluate effectiveness.

Implementation outcomes[38] will assess facility-level adoption and the fidelity of implementation of each intervention component.

Patient-related outcomes measures relating to diabetes will be conducted to translate and validate questionnaires in Guatemalan Spanish and Mayan Kaqchikel. Measures include diabetes distress, quality of life, and self-care assessments. We will use validated Spanish or professionally translated Mayan language versions of each instrument. These assessments are exploratory to refine the study team's use of these instruments in rural Guatemala.

Table 3: Outcomes and data sources

Outcome	Description and data sources
Primary outcomes	
Feasibility	FIM questionnaires and MOH data from DHIS2 (quantitative); semi-structured interviews with MOH participants (qualitative)
Acceptability	AIM questionnaires and MOH data from DHIS2 (quantitative); semi-structured interviews with patient and MOH participants (qualitative)
Secondary outcomes	
Clinical outcomes	

Table 3: Outcomes and data sources

Outcome	Description and data sources
Number of patients receiving hypertension medication treatment per month ("hypertension treatment rate")	MOH data from SIGSA (quantitative)
Number of patients receiving diabetes medication treatment per month ("diabetes treatment rate")	MOH data from SIGSA (quantitative)
Proportion achieving glycemic control (FBG <115 mg/dl or RBG <160 mg/dl) among patients with diabetes	MOH data from DHIS2 (quantitative)
Proportion achieving control of blood pressure (<130/80 mmHg) among patients with hypertension	MOH data from DHIS2 (quantitative)
Mean SBP and DBP among patients with hypertension	MOH data from DHIS2 (quantitative)
Implementation outcomes	
Adoption	Number of participating health facilities, defined as having enrolled at least one patient with hypertension or diabetes (quantitative); reasons for variation (qualitative)
Fidelity (health worker training on hypertension and diabetes treatment protocols)	Proportion of health workers in each district attending all training sessions, chart audit of prescriptions to assess guideline concordance (quantitative); reasons for variation (qualitative)
Fidelity (team-based care and task sharing)	Proportion of primary health districts conducting at least one care coordination meeting; reasons for variation (qualitative)
Fidelity (access to medicines and diagnostics)	Monthly availability of MOH medications and diagnostics (quantitative) and reasons for variation (qualitative)
Fidelity (facility-based electronic monitoring tool)	Proportion of patient visits captured in DHIS2 each month compared to comprehensive records in SIGSA (quantitative) and reasons for variation (qualitative)
Fidelity (systems monitoring and feedback)	Proportion of quarterly reports viewed by health district administrators (quantitative) and reasons for variation (qualitative)
Usability (facility-based electronic monitoring tool)	System Usability Scale[41,42] (quantitative) and reasons for variation (qualitative)
Sustainability	Program Sustainability Assessment Tool (PSAT)[43,44] and Clinical Sustainability Assessment Tool (CSAT),[45,46] select questions

Table 3: Outcomes and data sources

Outcome	Description and data sources
Patient-related outcomes measures	
Diabetes distress	Diabetes Distress Scale (DDS),[47,48] 2-item screening and physician distress subscale
Disability	WHO Disability Assessment Schedule (WHODAS 2.0)[49]
Multimorbidity treatment burden	Multimorbidity Illness Perceptions Scale (MULTIPleS),[50,51] treatment burden subscale

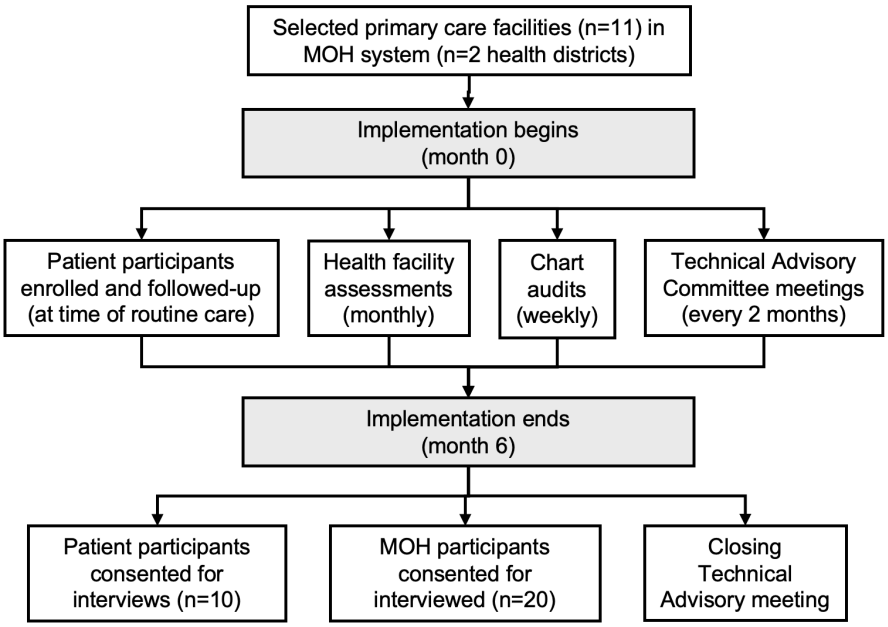
Abbreviations: CSAT: Clinical Sustainability Assessment Tool; DBP: diastolic blood pressure; DHIS2: District Health Information System; FBG: fasting blood glucose; MOH: Ministry of Health; PSAT: Program Sustainability Assessment Tool; RBG; random blood glucose; SBP: systolic blood pressure; SIGSA: Health Management Information System; WHO, World Health Organization.

7. STUDY PROCEDURES

7.1. Study overview

A summary of study procedures is shown in **Figure 3**.

Figure 3: Schematic of study design



7.2. Recruitment and sampling

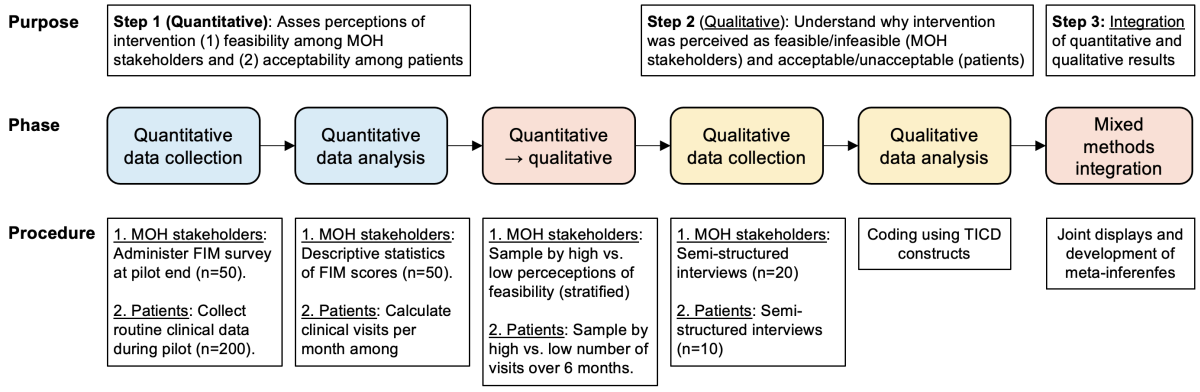
This project is embedded in MOH-led standard routine primary care services. All new or existing patients with diabetes or hypertension receiving care at the participating MOH primary care facilities will be enrolled in the DHIS2 system. Recruitment activities will be carried out that align with the routine outreach activities of each MOH health facility; these activities may include

meetings with local leaders, public posters, and brief announcements on social media platforms or the radio.

A subset of patient participants (n=10, of whom n=5 from each health district) will be recruited for questionnaire assessments and interviews. These patient participants will be purposively selected among individuals who had enrolled in the first two months of the study and had high versus low numbers of patient visits (i.e., explanatory sequential mixed methods sampling). Study fieldworkers who are not MOH employees will make an initial contact via home visit, phone calls, or encounters at MOH health facilities. Participants who express interest in this part of the study will then receive a visit by study fieldworks to complete informed consent and interview assessments. This visit will occur in the patient's home or another convenient private location, depending on the patient's preference.

All MOH participants and members of the Technical Advisory Committee will be asked to complete a structured questionnaire. The study team will use lists of personnel participating in trainings and contacts at each health district to identify MOH participants. Members of the Technical Advisory Committee will be recruited using INCAPs local contacts and connections from prior projects with the MOH. Subsequently, a subsample of approximately 20 MOH participants will be purposively selected for semi-structured interviews based on high versus low perceptions of intervention feasibility (i.e., explanatory sequential mixed methods sampling). Mixed-methods procedural diagrams are shown in **Figure 4**.

Figure 4: Mixed-methods procedural diagram



7.3. Study visits

7.3.1. Baseline visits at primary health care facilities

At baseline, study staff will visit all participating health centers and health posts to complete a baseline needs and readiness assessment based on HEARTS monitoring guidelines and the WHO Service Availability and Readiness Assessment tool.[22,37,52] Topics covered include population served, clinical services offered, available resources, staffing, and other topics relating to HEARTS.

7.3.2. Monthly follow-up visits at primary health care facilities

Study staff will conduct monthly follow-up visits at each primary health care facility to monitor the availability of medications and supplies, review patient registration in the DHIS system, assess implementation of collaborative care meetings, and provide support for any

implementation issues relating to HEARTS. Study fieldworkers will also maintain a field log with notes from primary health facility visits.

7.3.3. Closing interviews with diabetes patient participants

Interviews consisting of structured and semi-structured questions lasting approximately 45 minutes will be carried out with a subsample of approximately 10 patients with diabetes at the project's termination. The focus will be on diabetes, as the study team has conducted extensive interviews with hypertension patients in prior HEARTS-aligned projects. The structured portion will cover patient reported outcome measures, and the semi-structured portion will cover to acceptability and determinants of implementation (i.e., barriers and facilitators). The Tailored Implementation in Chronic Diseases (TICD) checklist will guide the semi-structured interviews.[53] Visits will be carried out in-person the patient's home or another convenient location. Interviews will be in Kaqchikel, Tz'utujil, or Spanish.

7.3.4. Closing interviews with MOH health workers and administrators

All MOH participants participating in the pilot will be invited to complete a structured questionnaire, focusing on feasibility (FIM instrument), sustainability (PSAT/CSAT instrument), and usability of the facility-based electronic monitoring tool (System Usability Scale). Additionally, a subsample of approximately 20 MOH staff will be purposely selected to participate in semi-structured interviews lasting approximately 45 minutes. The TICD checklist will guide the semi-structured interviews.[53] Interviews may be conducted in-person or virtually.

7.3.5. Technical Advisory Committee meetings

We will establish a Technical Advisory Committee to provide high-level coordination with national authorities, as recommended in the HEARTS implementation guide.[22] The Technical Advisory Committee will play a critical role to provide guidance and to plan for future scale-up. Members will likely include MOH administrators at the national, departmental, and health district levels; physicians and professional nurses working in each health district, representatives of the Guatemalan PAHO office, and other stakeholders (10-15 total members). Study staff at INCAP will organize meetings every two months during the trial and a post-trial closing meeting. Meetings will be conducted virtually and will be recorded for members who cannot attend a given session. Written meeting notes also will be shared after each session.

During the meetings, study staff will present project updates for open discussion. Using an implementation mapping approach,[54] members then will discuss the implementation determinants (i.e., barriers and facilitators) that emerge during the trial, design implementation strategies to address these determinants, clarify the causal mechanisms through which implementation strategies operate, and provide feedback on a consolidated implementation package the study team creates after the trial concludes. Study staff will guide discussions of implementation strategies using different structured tools:

- The Expert Recommendations for Implementing Change (ERIC) compilation and prior mappings of ERIC to lower-middle-income countries will be used as a foundation for proposed implementation strategies.[55,56]
- Guidance from Proctor et al. will be used to specify implementation strategies.[57]
- The APEASE (acceptability, feasibility, effectiveness, cost-effectiveness, side effects or unintended consequences, safety, and equity) tool will be used to prioritize implementation strategies.[58]

- Causal pathway models will be presented to link implementation strategies, mechanisms, and key implementation outcomes.[59,60]

7.3.6. Chart audits

Each week, a data manager will review all new data entered into the DHIS2 system for missingness and errors. Physicians on the study team also will perform a clinical audit of at least 25% of patient visits. The physicians will use a structured checklist to rate the guideline-concordance of clinical care and adequacy of data entry.

7.4. Data collection and management

Data will be collected using different collection methods.

- Clinical data from patient participants will be entered into DHIS2 by MOH health workers who provide standard clinical care during routine visits. DHIS2 data are stored on INCAP's server, as approved by the MOH.
- Data from structured assessments will be collected electronically using a cloud-based version of REDCap hosted at INCAP. Structured assessments include health facility monitoring, chart audits, and questionnaire data from closing interviews with patients and MOH staff. Data entry and quality control checks will be performed by study staff on all structured data entered into REDCap
- Qualitative data from semi-structured interviews will be collected in the field by a trained qualitative researcher on the study team. Other qualitative data will include field notes, meeting notes, and study team reflections implementation progress and challenges.[61] Qualitative data will be securely stored on the University of Michigan's institutional Dropbox account with routine back-ups to an encrypted hard drive.

8. SAMPLE SIZE CONSIDERATIONS

Primary health facilities. The sample of health facilities will include nine health posts and 2 health centers for a total 11 primary health facilities. No formal sample size calculation was performed.[62,63] This sample of health facilities and population size of pilot health districts is consistent with recommendations in the HEARTS Implementation Guide.[22]

Table 4: Semi-structured interview sample

Actor	Number[a]
Participants with diabetes	10
MOH physicians or physicians-in-training	4
MOH professional nurses	4
MOH auxiliary nurses	10
MOH administrators	2
Total	**30**

[a]The interview sample will be stratified by sex (target of 50% men and women by actor) and by health district (target of 50% from each health district).

Patient participants. The target sample of patient participants will be approximately 100 individuals, or 50 participants per health district. Based on the study team's prior experience, the

anticipated breakdown is n=45 patients with hypertension only, n=45 with diabetes only, and n=10 patients with both hypertension and diabetes. However, it is possible that the improved clinical services may attract a greater number of patients to MOH care than anticipated for the pilot. Of these, a subsample of 10 participants with low versus high retention levels (defined by number of clinical visits within the study time period) will be selected for semi-structured interviews at the close of the study. To improve understanding of how diabetes can be integrated into the HEARTS hypertension primary care model, we will purposely sample patient participants with diabetes.

MOH participants. The anticipated sample of MOH participants working to implement HEARTS will be approximately 50 participants. Of these, a subsample of 20 will be selected for semi-structured interviews at the close of the study using the breakdown shown in **Table 4**.

Including patient and MOH participants, a total of 30 semi-structured interviews are planned to achieve thematic saturation.[64,65] The interview sample will be sex-stratified with a target of 50% men and women by actor. Interviews will be analyzed as they are conducted, and more may be added if saturation is not achieved.[66]

9. ANALYSIS PLAN

Quantitative analysis: Questionnaire data will be analyzed using descriptive statistics. Clinical data will be analyzed using multilevel linear and logistic regression models of individual-level data adjusting for clustering of participants within primary health facilities. Sociodemographic variables such as age, sex, education level, and other characteristics may be explored in regression models if sample sizes permit. Stata will be used for quantitative analyses.

Qualitative analysis: Semi-structured interviews will be recorded and analyzed in Spanish using qualitative directed-content analysis.[67,68] We will only transcribe recordings if the interview were undertaken in a Mayan language (Kaqchikel or Tz'utujil), in which cases professional linguists will translate and transcribe into Spanish for analysis. Constructs from the Tailored Implementation in Chronic Diseases checklist will guide qualitative coding.[53] Two members of the research team proficient in Spanish will independently code transcripts, and the PI will reconcile differences.

Mixed methods analysis of primary outcomes: Quantitative and qualitative findings of primary outcomes will be integrated using joint displays, which are a mixed-methods visual technique.[69] Joint displays will show quantitative data next to illuminating participant quotes. Examination of quantitative, qualitative, and mixed-methods data will permit the study team to draw meta-inferences regarding the projects' feasibility and facilitate future implementation planning.

10. DATA AND SAFETY MONITORING PLAN

10.1. Adverse event reporting

Because the proposed research is considered no more than minimal risk, adverse events (AEs) related to the proposed strategies are not anticipated. The intervention in this study is focused on improving standard-of-care treatment of diabetes or hypertension delivered by the MOH health workers in MOH facilities. Therefore, it will be the responsibility of the MOH staff to provide care for patient participants who experience an adverse event (e.g., hypotension, hypoglycemia, or other adverse drug effects as noted in 11.3) to manage these patients according to MOH protocols. In our reporting role, the study team will review from MOH records

all serious AEs, unanticipated problems, and other reportable information or occurrence (ORIO) using an event form and reported using to the University of Michigan IRB using the standard timetable and grading scale, consistent with federal guidelines.[70]

10.2. Monitoring the study

The study team will conduct monthly scheduled assessments of study recruitment, data integrity and quality, adverse events, withdrawals, and compliance with protocol. Research staff and MOH staff will be instructed to report in person or by telephone all complaints, protocol deviations, or unanticipated problems to the study coordinators. The study coordinator will be charged with gathering necessary information from this initial report and contacting the PI at the time of the event. No interim analyses are planned. The trial will not employ stopping rules or a Data Safety Monitoring Board because the study carries no more than minimal risk to participants. If there is available funding and the study investigators and Technical Advisory Committee think there would be potential benefit in extending the pilot trial, then an extension to may be considered (e.g., from 6 months to 12 months in duration).

11. ETHICAL AND OVERSIGHT CONSIDERATIONS

11.1. Plan for multiple IRBs

For this project, the study team will pursue ethics approval from the IRB of the Ministry of Health in Guatemala, as well as the IRBs at INCAP and the University of Michigan. Protocol revisions will be submitted for approval by all three IRB committees.

11.2. Study coordination with MOH

This study will be tightly coordinated with the MOH and other authorities through Technical Advisory Committee (TAC) meetings (Section 8.1.5).

11.3. Potential risks

This study involves a multilevel, multicomponent intervention to improve standard care of hypertension and diabetes at MOH primary care facilities in Guatemala. All clinical care will be provided in accordance with existing MOH protocols, by MOH health workers, in MOH-operated primary health facilities. There is no control arm. Participants include both patients receiving standard care and MOH staff who deliver or supervise standard care. The risks in participating in this study are no more than minimal because the probability and magnitude of harm or discomfort are not greater than those ordinarily encountered in routine daily life:

Psychological risks: Participants invited to participate in structured and semi-structured interviews may experience minor stress or discomfort answering certain questions. An example of a potentially uncomfortable topic for MOH participants may include interview questions relating to the quality of MOH care. An example of a potentially uncomfortable topic for patient participants might be questions about medical history, quality of life, or experiences of discrimination or abuse in the health system. We will protect against this risk by reminding participants that they can skip questions or end interview participation at any time. All research staff will complete and provide proof of completion of appropriate human subjects protection training approved by their home institution.

Risk of lost personal productivity due to the time burden of participation: Structured and semi-structured interviews are structured to last 45 minutes but may last 60 minutes or longer. Participants invited to participate in these interviews may perceive this time involvement to be a burden interfering with their other responsibilities. We will protect against this risk by offering flexible appointments for interviews, including on evenings or weekends. The study team also will be available to coordinate study visits at participants' homes or another private location requested by participants.

Loss of confidentiality risks: There is the unlikely risk of accidental disclosure of confidential data. Currently, Guatemala does not have a specific national regulation on electronic medical records or telemedicine cybersecurity.[71] To protect against breach of confidentiality, all non-clinical patient data will be maintained using a unique study identification. Structured data will be securely collected using REDCap on an encrypted tablet and stored on INCAP's secure cloud server. Qualitative data from semi-structured interviews will be collected using an encrypted mobile device and stored on the University of Michigan's institutional Dropbox account. An electronic spreadsheet with the unique identification numbers will be maintained on the U-M's institutional Dropbox account, and only the PI and study coordinators will have access. Clinical patient data usually will be entered into the DHIS2 tool by MOH staff during routine clinical visits. Some MOH primary facilities may choose an asynchronous strategy in which patient data are collected using paper records and entered into DHIS2 after the routine clinical visit. These paper forms will be stored in a locked filing cabinet in a locked room at the MOH facility. The DHIS2 system will be hosted on an INCAP's secure cloud server. Password-access to DHIS2 will be restricted to relevant MOH staff, the PI, and study coordinators.

Physical risks to patient participants: A potential risk to blood glucose collection might include adverse response to a capillary blood draw, including lightheadedness, minor bleeding, or infection at the lancet site. A potential risk to patients receiving diabetes or hypertension medication treatment might include hypotension, hypoglycemia, or other adverse drug effects that have previously been described. To protect against these risks, all patients enrolled in the trial who experience these symptoms will be managed at the nearest MOH facility by MOH health workers according to national guidelines. This risk will be no higher than standard care because prescriptions will be made by MOH health workers using available medications with known, widely accepted safety profiles. The antihypertensive medications used by MOH health workers in primary health facilities include hydrochlorothiazide, enalapril, and losartan. The glucose-lowering agents used by MOH health workers include metformin and glimepiride. Insulin, which confers a higher risk of hypoglycemia, will not be used in this study because it is not available in MOH health centers or health posts.

11.4. Potential benefits

Patient participants will benefit from improved hypertension and diabetes services at MOH primary health facilities. Based on MOH guidelines, tangible patient benefits include free access to oral antihypertensive and glucose-lowering medications, glucose and blood pressure monitoring, receipt of care from health workers who have received additional training in hypertension and diabetes, and other benefits.

MOH participants will benefit mostly indirectly from this project through their altruism in helping to improve the implementation of hypertension and diabetes care in Guatemala. They also will receive training on clinical management of these diseases, which may contribute to their job satisfaction and professional development.

11.5. Informed consent

11.5.1. Patient participants receiving MOH standard clinical care

Informed consent will not be obtained from patient participants receiving routine care at MOH primary care facilities. A waiver of informed consent is justified because the research meets all five required criteria in the revised Common Rule.[72]

1. The research involves a single-arm trial of improving the implementation of standard care in the MOH, and as such the trial confers no more than minimal risk.
2. The research could not practicably be carried out without an informed consent waiver. There are a few reasons why this is the case. The intervention to be tested will be embedded in standard care across 11 geographically distant MOH primary health facilities. It is not feasible to hire full-time study staff to be physically present at all health facilities to consent potentially eligible patients. There is no appointment system in the MOH, so it would not be practical to coordinate patient clinical encounters with visits from study staff. It would not be ethically practical to restrict access to MOH standard care based on the availability of study staff to consent patients.
3. This research requires identifiable private information because a key component of the intervention is the implementation of a health facility monitoring tool with individual-level data used in routine care by MOH clinicians. As such, the research could not be practicably carried out without using such information or biospecimens in an identifiable format.
4. The research will not adversely affect the rights and welfare of patient participants receiving routine MOH-led care.
5. Participants and their clinicians will be provided with pertinent written information during the trial. This information will include instructions on how patient participants can contact study staff to request that their data not be included in research outputs of the project.

11.5.2. Patients and MOH staff participating in interviews

Verbal consent will be obtained from participants interviewed at the study conclusion and from stakeholders participating in the Technical Advisory Committee and. A study staff will read the consent script, which explains the purpose of the study, mentions that ongoing clinical care (in the case of patients) or employment (in the case of MOH participants) is not conditional on participation in the study, and reiterates that there will be no repercussions for declining to participate in the study. Verbal consent procedures will occur in the language of the participant's choosing. All MOH participants speak Spanish proficiently, but some patient participants may prefer a Mayan language. In lieu of written documents in Mayan languages, we will use extensive preparatory practice sessions to ensure smooth contemporaneous translation from Spanish to Mayan. This is the method that we have used in Guatemala for many years on numerous prior projects, including large projects funded by NIH. Once verbal informed consent is obtained, the study staff member will record the date of verbal consent on the informed consent form, sign the form, and provide a copy of the form to the participant either as a physical copy (in-person interviews) or an electronic copy (virtual interviews).

11.6. Post-trial care

This trial is embedded in standard MOH primary care. All patient participants will be able to continue receiving diabetes or hypertension care according to national standards after the study

closes. Depending on patient volume and logistics in the MOH, some health posts participating in the trial may refer patients to health centers for continuation of care.

12. DISSEMINATION OF RESULTS AND SCALE-UP PLANNING

Project results will be shared through a structured dissemination strategy that includes the following components:

- Information about this study will be shared via timely registration, updates, and results reporting on ClinicalTrials.gov.
- Project results will be shared with patient and MOH participants through a meeting in each health district at the end of the project. MOH stakeholders will also have results disseminated through the TAC.
- The investigators will disseminate findings at academic research conferences and in peer-reviewed journal articles. Open access journals will be prioritized for publication. Eligibility for authorship on academic products will be guided by International Committee of Medical Journal Editors guidelines.
- A non-technical report in Spanish and English will be prepared and shared with representatives from the MOH, PAHO, and INCAP's Board of Directors (who include the Ministers of Health of the eight countries of the Central American region). This report will include an implementation toolkit for integrated hypertension and diabetes care.
- Findings also will be disseminated through established non-communicable disease research and policy networks in which INCAP participates.

The study investigators and HEARTS stakeholders also will use results for implementation and scale-up planning. Issues to be considered will be a phased versus national approach, funding, how to incorporate implementation strategies into operative plans, and other topics outlined in the HEARTS Implementation Guide.[22] It also will be important to consider research designs to balance causal estimates while balancing ethical and practical considerations of HEARTS implementation in the Guatemalan context.[73]

13. DATA SHARING

This project will produce multiple types of data, including patients' clinical information, health facility assessments, and structured and semi-structured interviews. Deidentified data, analytic code, and data dictionaries will be made available on the NHLBI BioLINCC data repository (https://biolincc.nhlbi.nih.gov/) after the study concludes. Semi-structured interview transcripts and structured questionnaire data will not be shared due to privacy concerns and risk for re-identification.

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15. SUPPLEMENTARY FILES

The following supplementary files are included with this protocol.

1. Spirit checklist
2. DHIS2 visit forms
3. Baseline health facility assessments
4. Follow-up health facility assessments
5. Chart audit form
6. Technical Advisory Committee meetings agenda and discussion prompts
7. Structured questionnaire and semi-structured interview guide for patient participants
8. Structured questionnaire for MOH participants
9. Semi-structured interview guide for MOH participants
10. Consent form: Patient and MOH participants who are interviewed
11. Consent form: Technical Advisory Committee members
12. Patient participant handout at primary health facilities
13. Poster at health facilities