**PROTOCOL TITLE:** Transforming Hypertension Treatment in Nigeria using a Type II Hybrid, Interrupted Time Series Design - Aims 2 & 3

**NATIONAL CLINICAL TRIAL (NCT) IDENTIFIER:** *Pending*

**GRANT NUMBER:** R01HL144708

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**VERSION NUMBER:** 1

**VERSION DATE: 1**5 January 2026

**STATEMENT OF COMPLIANCE:**
This trial will be conducted in compliance with this protocol, International Council on Harmonization Good Clinical Practice (ICH GCP) and applicable local and federal regulatory requirements. The protocol and any other participant-facing materials will be submitted for review and approval by Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as well as relevant local institutional ethics committees.

The protocol, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before any participant is recruited. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

**INVESTIGATOR'S SIGNATURE:**
*The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the Statement of Compliance above.*

**Principal Investigators:**

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**PROGRAM SUMMARY:**

| | |
|---|---|
| Investigational Agent(s) (Drugs or Devices) | None |
| IND / IDE / HDE # | NA |
| Indicate Special Population(s) | ☐ Children<br>☐ Children who are wards of the state<br>☒ Adults Unable to Consent<br>☒ Cognitively Impaired Adults<br>☐ Neonates of Uncertain Viability<br>☒ Pregnant Women<br>☐ Prisoners (or other detained/paroled individuals)<br>☐ Students/Employees |
| Sample Size | Aim 2: 10,000 participants<br>Aim 3: 2,800 participants |
| Funding Source | National Heart, Lung, and Blood Institute |
| Indicate the type of consent to be obtained | ☐ Written<br>☐ Verbal/Waiver of Documentation of Informed Consent<br>☐ Waiver of HIPAA Authorization<br>☒ Waiver/Alteration of Consent Process |
| Site | ☒ Lead Site (For A Multiple Site Research Study)<br>☐ Data Coordinating Center (DCC) |
| Research Related Radiation Exposure | ☐ Yes<br>☒ No |
| DSMB / DMC / IDMC | ☒ Yes<br>☐ No |

## 1. OBJECTIVES

The purpose of the second phase of the Hypertension Treatment in Nigeria (HTN 2.0) Program is to build upon the success of the first phase of the HTN Program (2020-2023), which implemented the WHO HEARTS package across 60 primary healthcare centers (PHCs) in the Federal Capital Territory (FCT). This program demonstrated significant improvements in hypertension treatment and control. HTN 2.0 will evaluate sustainment of hypertension control in the Federal Capital Territory and will expand implementation of the HEARTS bundle to 5 new states in 5 geopolitical zones in Nigeria (Abia, Delta, Gombe, Jigawa, and Oyo). Additionally, diabetes management will be included through the implementation of the HEARTS-D bundle in 10 PHCs across the FCT that previously participated in the initial HTN Program. Overall, the

objective of this study is to evaluate the effectiveness of program implementation on hypertension and diabetes management in Nigeria.

This protocol represents the activities that will be carried out to implement and evaluate effectiveness and implementation outcomes of a system-level hypertension and diabetes control program among patients with hypertension and diabetes through an interrupted time series design to improve hypertension and diabetes treatment and control at system and patient levels. This system-level hypertension control program is modeled after Kaiser Permanente's Northern California (KPNC) Hypertension Program and the World Health Organization (WHO) HEARTS package as exemplars for large-scale hypertension control.[13] This package was implemented as part of the first phase of the Hypertension Treatment in Nigeria Program in the Federal Capital Territory.

## 2. BACKGROUND

Elevated blood pressure and glucose are two leading modifiable risk factors for global cardiovascular disease (CVD) morbidity and mortality, including in Nigeria, the most populous country in sub-Saharan Africa.[7,18,25] In Nigeria, the age-adjusted adult prevalence of hypertension and diabetes mellitus is estimated to be 36% and 3.6%, respectively.[11,32] Despite the large and growing burden of these two conditions, awareness, treatment, and control rates for both remain very low.[11,18] During the initial funding period of this award, our team contextualized, implemented, and evaluated implementation and effectiveness of a multilevel bundle of strategies to integrate hypertension services in 60 public, primary healthcare centers (PHCs) in the FCT of Nigeria using a type II hybrid, interrupted time series design.[2,22] The bundle, adapted from the WHO HEARTS technical package, included: 1) a hypertension patient registry with empanelment, 2) a simplified, national treatment protocol emphasizing upfront fixed-dose combination therapy, 3) team-based care led by community health extension workers (CHEWs), 4) quarterly site supervision with monthly performance and quality reporting, and 5) reliable access to quality essential medicines and technology supported by a drug revolving fund to lower out-of-pocket costs. **From January 2020 to December 2023, we recruited 21,897 adults (142,249 visits) with hypertension from 60 sites and demonstrated a remarkable improvement in 6-month rolling average of hypertension control (i.e., blood pressure <140/<90 mmHg) from 22% to 56%. The program showed a sustained hypertension control rate >50% for nearly 2 years, through the end of follow-up**. Our detailed implementation assessment, including how HEARTS was normalized into routine care, provides a roadmap for scale-up.

We have organized an exceptional group of national, state, and local partners in Nigeria, including government health agencies and policymakers, healthcare providers, professional bodies, and an advisory board who now co-own this work for this second phase of the program. Our collaborators have called on us to develop an updated protocol that includes scale-up of hypertension services aligned with national priorities, specifically related to Nigeria's emerging community insurance, basic healthcare provision funds, and health management information systems[1], as well as integration of diabetes services in public primary care based on the HTN Program. We have conducted relevant preliminary work, including mixed methods assessments of our previous trial and preliminary readiness assessments for horizontal scale-up[4] for hypertension and diabetes.

In this protocol, we will use the Implementation Research Logic Model[28] to contextualize HEARTS and the diabetes module of HEARTS (HEARTS-D). We will also use WHO ExpandNet framework[31] and RE-AIM framework [8,29] embedded within the Implementation Research Logic Model to guide and evaluate implementation and effectiveness of horizontal scale-up of the HEARTS bundle in 5 new states in 5 geopolitical zones in Nigeria. We will evaluate

effectiveness and the process implementation of the HEARTS-D bundle implementation on diabetes screening, diagnosis, treatment, and control in 10 PHCs in the FCT where we have previously integrated hypertensive services during the first phase of this program. We will also explore sustainment of hypertension control in these 10 centers, as well as the other previously-enrolled centers using DHIS-2, the government's preferred health management information system.

**Formative Aim 1: Using the Implementation Research Logic Model, conduct mixed methods formative research to refine implementation pathways of the HEARTS and HEARTS-D bundles in Nigeria.**

The research activities for Formative Aim 1 are outlined in a separate protocol.

**Aim 2: Evaluate effectiveness (2a) and implementation (2b) of scale-up of the HEARTS bundle on hypertension control (<140/<90 mmHg) in 50 primary healthcare centers in 5 states in Nigeria using a type II hybrid, single arm interrupted time series design.**

*H2a: We hypothesize that HEARTS implementation will increase hypertension control more in the implementation period than the pre-implementation period ($1^o$ effectiveness outcome). Hypertension treatment, mean systolic and diastolic blood pressure will be $2^o$ effectiveness outcomes. Safety outcomes include rates of serious adverse events, adverse events of special interest, and laboratory abnormalities.*

*H2b: We hypothesize that the HEARTS bundle will reach the target population and will be adopted, implemented, acceptable, affordable, and maintained as intended. The primary implementation outcome will be the dose of quarterly supportive supervision visits measured by the proportion of observed/expected visits measured in the implementation period.*

**Aim 3: Evaluate effectiveness and implementation process of the HEARTS-D bundle on diabetes screening in 10 primary healthcare centers in Federal Capital Territory that have already implemented HEARTS.**

*H3: We hypothesize that the HEARTS-D implementation will increase diabetes screening more in the implementation period than the pre-implementation period ($1^o$ outcome). Diabetes treatment and control and mean fasting glucose will be $2^o$ effectiveness outcomes. Safety outcomes include rates of serious adverse events, adverse events of special interest, and hypoglycemia. We will also explore sustainment of hypertension control not only in these 10 sites but also in the other 50 sites in the Federal Capital Territory that implemented HEARTS during the first phase of the program using the District Health Information System -2 (DHIS-2).*

This protocol includes implementation and evaluation of a culturally- and contextually adapted implementation bundle based on the KPNC and WHO HEARTS programs for hypertension diagnosis, treatment, and control at public, primary health centers previously used in the Federal Capital Territory and now to be implemented in five expansion states (i.e., Abia, Delta, Gombe, Jigawa, Oyo). Implementation pathways have been developed with particular attention to overcoming modifiable system- and patient-level barriers to hypertension treatment and control across capability, intentional, and system domains using the updated Consolidated Framework for Implementation Research (CFIR 2.0, cfirguide.org). Readiness and capacity have been assessed at primary health centers (e.g. available staff; information systems; use of clinical guidelines) through an adapted Service Availability and Readiness Assessment (SARA) instrument during the formative work for this Program.

## 1. PROGRAM ENDPOINTS

Primary Effectiveness Outcome (Aim 2)

- Difference in the 6-month rolling average of hypertension control between the pre-implementation and implementation periods (defined as <140/<90 mm Hg)

Primary Implementation Outcome (Aim 2)

- Dose of quarterly supportive supervision visits measured by the proportion of observed/expected visits during the implementation period.

*Refer to the Research Plan for a detailed account of secondary and exploratory implementation outcomes.

Secondary Effectiveness Outcomes (Aim 2)

- Difference in the 6-month rolling average between the pre-implementation and implementation periods and will include:
    - Hypertension treatment
    - Mean systolic blood pressure
    - Mean diastolic blood pressure
    - Hypertension control (more stringent target), defined by blood pressure <130/80 mm Hg

Safety Outcomes

**Safety outcomes** will include between-period (pre-implementation versus implementation) differences in the proportion of:

- Serious adverse events
- Adverse events of special interest (i.e., clinically ascertained angioedema, syncope, lightheadedness/dizziness, edema, inappropriate medication prescription [e.g., ACE or ARB among patients who are pregnant])
- Hyperkalemia, hypokalemia, and acute kidney injury measured in a subset of 5 sites and 250 patients (n=500 total) in both pre-implementation and implementation periods.

*We will also assess for unanticipated problems to adhere to US federal regulations.

Definitions of Treatment and Control

Adults with hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg measured on two separate occasions or taking blood pressure lowering drugs) or adults with controlled (SBP <140 mmHg and DBP <90 mmHg) hypertension among those who are treated with blood pressure lowering drugs, will be continuously registered at participating primary healthcare centers. Once an individual is registered, they will be considered empaneled and will be asked to return regularly (e.g., monthly, quarterly) for follow-up monitoring and treatment at the primary healthcare center to achieve sustained hypertension control.

These analyses will assume the following for hypertension treatment (T) and control (C) at each month i (i=1…36) across all participating sites:

$$N_i = Number\ Newly\ Registered_i + Number\ Previously\ Registered\ Returned_i$$

The number of hypertensive registrants is defined as the number of patients with hypertension who are newly registered during any calendar month plus the total number of previously registered individuals who returned to primary health centers in that month for ongoing care.

Registrants who return for follow up care more than one time in a calendar month will be counted once for this analysis.

$$T_i = \frac{Number\ Newly\ Prescribed_i + \ Number\ Continuing\ BP\ Lowering\ Medication_i}{N_i}$$

Treatment will be calculated each month across all participating sites. Treatment is defined at a patient level as an ongoing or new prescription of any BP-lowering medication during the calendar month.

$$C_i = \frac{Number\ with\ SBP\ < 140\ mmHg\ and\ DBP\ < 90\ mmHg_i}{N_i}$$

Control will be calculated each month across all participating sites. Control is defined at a patient level as measured SBP <140 mm Hg and DBP <90 mm Hg during the calendar month. We will also evaluate a more stringent target (<130/<80 mm Hg) as a secondary outcome.

Refer to the Statistical Analysis Plan for further details on planned sensitivity and subgroup analysis.

Primary Effectiveness Outcome (Aim 3 )

- The **primary outcome** will be the difference in the 6-month rolling average of the diabetes screening among eligible patients, screening defined as a random plasma glucose screening among adults with symptoms of hyperglycemia or a fasting plasma glucose among adults ≥ 18 years old and body mass index ≥ 25 kg/m$^2$ in accordance with HEARTS-D, between the pre-implementation and implementation periods. Hemoglobin A1c may also be used if available.

**Symptoms of hyperglycemia include but are not limited to thirst, frequent urination, blurring of vision, fatigue, unintentional weight loss.*

Primary Implementation Outcomes (Aim 3)

- Dose of quarterly supportive supervision visits measured by the proportion of observed/expected visits during the implementation period.

Secondary Effectiveness Outcomes (Aim 3)

- **Secondary outcomes** will compare the 6-month rolling average of diabetes treatment, blood sugar control, and mean fasting glucose levels in the pre-implementation and implementation periods.

Safety Outcomes (Aim 3)

**Safety outcomes** will include between-period (pre-implementation versus implementation) differences in proportions of:

- Serious adverse events
- Adverse events of special interest (e.g., hypoglycemia, hyperglycemia, medication allergies, common medication side effects) in pre-implementation and implementation periods.

*We will assess for unanticipated problems to adhere to US federal regulations.

Definitions of Treatment and Control:

- Treatment will be defined by the prescription of any glucose lowering drug. Control will be defined according to the WHO HEARTS-D module[2], specifically: fasting glucose <126 mg/dl, postprandial glucose <160 mg/dl, or HbA1c <7%.

*Refer to research plan for additional details

## 2. PROGRAM INTERVENTION(S) / INVESTIGATIONAL AGENT(S)

The intervention is based on a culturally- and contextually adapted implementation bundle based on the KPNC, WHO HEARTS programs for hypertension diagnosis, treatment, and control, and WHO HEARTS-D programs for diabetes diagnosis, treatment, and control. The KPNC model, also based on the Hypertension Detection and Follow-up Study, includes 5 components.[10,13] The WHO HEARTS and WHO HEARTS-D package is based on 5 domains for hypertension and diabetes programming respectively.

| Component | KPNC Model | WHO HEARTS Model | WHO HEARTS-D | HTN 2.0 Program |
|---|---|---|---|---|
| Registry | HTN patient registration using baseline data collected in the formative period | HTN patient registration | Patient registry and empanelment | HTN and diabetes patient registration and longitudinal empanelment |
| Performance Reports | Monthly quality and performance reports, including treatment and control rates to sites | Information systems that allow for continuous, real-time program improvement | Information systems to support quality reporting and improvement. | Monthly automated quality and performance feedback reports. Real-time registry dashboard for patient follow-up |
| Simplified Treatment Guidelines & Patient Care | Simplified treatment guidelines<br><br>Use of fixed-dose combinations, such as lisinopril-HCTZ as first line treatment | Protocols that include specific medications, doses, and steps to streamline care and improve adherence and control<br><br>Use of fixed dose combinations<br><br>Patient-centered care with simpler medication regimens, no or reduced-cost medications and follow-up visits | Simplified treatment guidelines (see research plan)<br><br>Use of fixed-dose combinations, such as glibenclamide and metformin as first line treatment. | Simplified treatment guideline and national HTN consensus protocol<br><br>Federal Ministry of Health Diabetes Treatment Protocol for the Nigeria-Package of Essential Non-communicable Diseases (Nigeria-PEN) at the Primary Healthcare |
| Supply Chain | Streamlined medication options | Ensuring a reliable, uninterrupted supply of quality blood pressure lowering medicines | Access to functioning glucometers, test strips, and essential medicines supported by a drug revolving fund. | Supply chain strengthening through a drug revolving fund for blood pressure lowering drug availability and affordability |
| Non-Physician Care | Non-physician follow-up 2-4 weeks after medication changes | Use of non-physician health workers to prescribe, adjust, and intensify medication | Team based care and non-physician follow up. | Empowerment and enablement of CHEWs as first line for diagnosis, |

| | | | |
|---|---|---|---|
| | regimens based on physician orders and protocols | | treatment and management of patients with HTN and diabetes |
| Supportive Supervision | | Implementation strategy to provide guidance, mentorship, and resource allocation to healthcare workers to improve performance | Implementation strategy to provide guidance, mentorship, and resource allocation to healthcare workers to improve performance |

All drug classes are listed on the 2023 Nigerian Essential Medicines List and are recommended by the 2023 Nigerian standardized treatment guidelines for hypertension, including fixed-dose combination therapy (health.gov.ng). Nigeria has created a standard treatment guideline for hypertension, which will be the basis of the treatment protocol for the HTN Program. Nigeria also has a preliminary diabetes mellitus protocol: Diabetes Treatment Protocol for the Nigeria-Package of Essential Non-communicable Diseases (Nigeria-PEN) at the Primary Healthcare. Medication supply chain optimization will be supported by implementation of a drug revolving fund based on the study team's previous work.

## 3. PROCEDURES INVOLVED

**Aim 2: Evaluate effectiveness (2a) and implementation (2b) of horizontal scale-up of the HEARTS bundle on hypertension control (<140/<90 mmHg) in 50 primary healthcare centers in 5 states in Nigeria using a type II hybrid, single arm interrupted time series design.**

Pre-implementation period. At the start of the 12-month pre-implementation period, we will conduct one-day in-person training at the state level to implement a hypertension registry that captures relevant pre-implementation data. We will ensure that sites have functioning blood pressure monitors but will not include training related to hypertension diagnosis, treatment, and control to minimize the risk of contamination. We will not provide supportive supervision, nor will we implement a drug revolving fund during this period for similar reasons.

Implementation period. The 24-month implementation period will start when we conduct two-day in person training at the state-level based on the US Centers for Disease Control and Prevention Hypertension Management Training curriculum.[5] We used this program for the Hypertension Academy (n=575 participants) during the initial funding period. This program includes didactic, group-based, and hands-on education and training to promote knowledge and skill transfer, which will be measured during pre- and post-training assessments based on levels 1 (reaction), 2 (learning), and 3 (behavior) of the Kirkpatrick framework.[15] Implementation training will also be conducted with pharmacists to promote appropriate dispensation of medications and drug revolving fund implementation. During the implementation period, sites will receive quarterly in-person site supervision visits by trained members of the study team to provide ongoing training and support. In limited instances where there are security concerns at PHCs, remote or centralized training will be used, as we have previously done. Health workers who are not directly involved with the study will have the opportunity to participate in additional virtual training through mDoc, and in-person training through the Hypertension Academy led by Dr. Ojji, which will be available during Years 4-5. Co-I Baldridge will contribute to training assessments and analyses based on her previous experience.[3]

Primary healthcare centers will transition from the pre-implementation to implementation period by receiving monthly automated quality and performance feedback reports, real-time

dashboarding, simplified treatment guidelines, hypertension protocols, non-physician follow up after medication changes, supportive supervision, and implementation of a drug revolving fund. Transition from baseline to implementation period may be asynchronous within and between primary healthcare centers. The components of the baseline and intervention periods are considered standard of care.

Patients will be registered in a longitudinal hypertension registry regardless of study phase. Upon the first diagnosis of hypertension, or visit to the PHC during the registration period, participant data will be captured in the participant treatment card by a healthcare worker at the PHC. The participant will be administered a hypertension treatment card including vitals and a unique program identifier. The participant will be instructed to bring this card with them to subsequent visits for purposes of tracking their blood pressure over time. A participant treatment card will also be retained by the PHC to capture baseline and longitudinal participant information including demographics, contact information, medical history, blood pressures, laboratory measures, hypertension medications and adverse events. The data comprise information that would typically be found within a medical record. Patient treatment cards will be updated at each subsequent visit with blood pressures, changes in medication, new laboratory values, and adverse event information.

Registry data will be abstracted to REDCap either by a primary healthcare worker (e.g. record officer) at the PHC or by a member of the research team. The PHC may choose to transition to electronic data collection during the program after consultation with the research team.

Primary healthcare centers will transition from the pre-implementation to the implementation period between 9-15 months of baseline data collection. Transition to the implementation period will be considered initiated upon completion of hypertension training including review and provision of simplified treatment guidelines and hypertension protocols. After training completion, the primary healthcare center will begin receiving monthly automated quality and performance feedback reports, supportive supervision, and a drug revolving fund. Sites may also implement a real-time registry dashboard using REDCap. The dates of initiation of each bundle component at each primary healthcare center will be captured.

Participant data will be continuously monitored by both the primary healthcare center and the research team using centralized data monitoring. Participant data will be reviewed at minimum monthly by the research team, including review of all adverse events. The components of the pre-implementation period are considered standard of care.

**Treatment Steps:**

Protocol 1

1. If BP ≥ 140/90 mmHg: Start amlodipine 5 mg
2. After 1 month, measure BP, if still high treat with amlodipine 5 mg + losartan 50 mg
3. After 1 month, measure BP again. If still high treat with amlodipine 10 mg + losartan 100 mg
4. After 1 month, measure BP again. If still high treat with amlodipine 10 mg+ losartan 100 mg + HCTZ 25 mg.
5. After 1 month, measure BP again. If still high refer to specialist hypertension management

*If initial BP ≥ 160/100 mg, but <180/110 mmHg, start at step 2
*If initial BP ≥ 180/110 mmHg, give step 3 drugs and refer to emergency unit of nearest general hospital within 1 hour

Notes:

- Single pill combination of amlodipine plus losartan is preferred to free combination
- HCTZ= Hydrochlorothiazide
- Telmisartan 40 mg and 80 mg if available is preferable to losartan
- May substitute HCTZ 25 mg with amiloride, 2.5 mg/HCTZ 25 mg if HCTZ is unavailable

**If medication cost is a factor impacting availability or accessibility of the medications listed in protocol 1, protocol 2 may instead be used.*

Protocol 2:

1. If BP ≥ 140/90 mmHg: Start amlodipine 5 mg
2. After 1 month, measure BP, if still high treat with amlodipine 5 mg + moduretic ½ tablet (amiloride 2.5 mg + HCTZ 25 mg).
3. After 1 month, measure BP again. If still high treat with amlodipine 10 mg + moduretic ½ tablet (amiloride 2.5 mg + HCTZ 25 mg).
4. After 1 month, measure BP again. If still high refer to specialist hypertension management

*If initial BP ≥ 160/100 mg, but <180/110 mmHg, start at step 2
*If initial BP ≥ 180/110 mmHg, give step 3 drugs and refer to emergency unit of nearest general hospital within 1 hour

Notes:

- Single pill combination of amlodipine plus losartan is preferred to free combination
- Telmisartan 40 mg and 80 mg if available is preferable to losartan
- May substitute HCTZ 25 mg with amiloride 2.5mg/HCTZ 25 mg if HCTZ is unavailable
- Moduretic ½ tablet (amiloride 2.5mg/HCTZ 25 mg)

**Aim 3: Evaluate effectiveness and implementation process of HEARTS-D bundle on diabetes screening in 10 primary healthcare centers in Federal Capital Territory that have already implemented HEARTS.**

Summary. This aim uses an interrupted time series design to compare diabetes screening, diagnosis, treatment, and control between the pre-implementation (12 months) and implementation (24 months) periods in 10 primary healthcare centers in the Federal Capital Territory. These sites have already demonstrated the ability to register, empanel, treat, and control patients with hypertension during the first phase of the study, which will continue during this second phase. These sites will expand their service provision to include the diabetes module through HEARTS, also known as HEARTS-D.

Pre-implementation period. At the start of the 12-month pre-implementation period, we will conduct one-day in-person training at the state level to implement a diabetes and diabetes screening registry that captures relevant pre-implementation data. We will ensure that sites have functioning glucometer and test strips but will not include training related to diabetes diagnosis, treatment, and control to minimize the risk of contamination. We will not provide supportive supervision, nor will we implement a drug revolving fund.

Implementation period. The 24-month implementation period will start when we conduct two-day in person training based on the HEARTS-D curriculum[33] with least 2 health care workers (physician, nurse, community health extension worker, pharmacist) and 1 record officer at each of the 10 sites. We will assess pre-/post-training test scores to evaluate knowledge transfer. Sites will receive an initial stock of supplies aligned with the WHO Package of Essential Noncommunicable Disease Interventions for Primary Care (e.g., functioning glucometer, test strips, and glucose lowering medications).[34] We will also expand the existing drug revolving fund[41] at these 10 sites, which currently supports accessibility (i.e., availability + affordability) of blood pressure lowering drugs, to include metformin and glibenclamide. Similar to our work on hypertension, this approach aligns with Nigeria's national guidelines for drug revolving fund operations.[19] Sites will also receive quarterly supervision for diabetes and hypertension care, similar to how we have conducted this in the first phase of the program. These visits allowed the research team to provide quality reports, monitor bundle implementation, evaluate screening and diagnosis rates compared with clinic logs, and adapt and problem-solve based on site-specific challenges.

**Screening and Diagnosis**
All adults 18 years of age or older showing signs of hyperglycemia, OR all adults aged 18 years of age or older who are overweight (BMI $\geq$ 25 kg/m$^2$) will be screened for diabetes.

- Normal:
  - Fasting blood glucose < 5.6 mmol/L
  - Random blood glucose < 7.8 mmol/L

- Pre-Diabetes
  - Fasting blood glucose >5.6 mmol/L but < 7.0 mmol/L
  - Random blood glucose >7.8 mmol/L but < 11.2 mmol/L

- Diabetes:
  - Fasting blood glucose ≥ 7.0 mmol/L
  - Random blood glucose ≥ 11.1 mmol/L

If the participant does not have previously diagnosed diabetes but has a fasting blood glucose or random blood glucose reading in the diabetes range, then a follow up fasting blood glucose reading will be obtained either the next day (for PHC's that have daily diabetes testing capabilities) or on the second/third day (for PHC's that do not have daily diabetes testing capabilities). Two abnormal blood glucose values will be required for a diabetes diagnosis and participation in this study. On the other hand, repeat testing for a diabetes diagnosis is not required for patients with unequivocal hyperglycemia defined as patients having a random plasma glucose ≥ 11.1 mmol/L and symptoms consistent with hyperglycemia (polyuria, polydipsia, etc.).

**Treatment Steps**
*Uncontrolled blood glucose is defined as random blood glucose levels exceeding 11.1 mmol/L while receiving treatment.

Step 1
- Indication: Random blood glucose at diagnosis is ≥ 11.1 mmol/L but < 11.7 mmol/L
- Treatment: Metformin 500 mg once daily
- Action: Review after 1 month. If uncontrolled then proceed to Step 2

Step 2
- Indication: Random blood glucose ≥ 11.7 mmol/L
- Treatment: Metformin 1000 mg once daily
- Action: Review after 1 month. If uncontrolled, then proceed to Step 3

Step 3
- Indication: Random blood glucose ≥ 13.3 mmol/L
- Treatment: Metformin 1000 mg twice daily
- Action: Review after 1 month. If uncontrolled, then proceed to Step 4

Step 4
- Indication: Random blood glucose ≥ 16.7 mmol/L
- Treatment: Metformin 1000 mg twice daily + Glibenclamide 5 mg once daily (Increase Glibenclamide gradually to max 15 mg daily)
- Action: Review after 1 month. If still uncontrolled, then proceed to Step 5

Step 5 – Referral Criteria

Refer to higher-level care or specialist if any of the following apply:
- Uncontrolled after Step 4
- Pregnancy
- Vision impairment (e.g., cataracts, retinopathy)
- Peripheral neuropathy (numbness, tingling, burning)
- Leg ulcers or infections
- Proteinuria defined as ≥1+ on dipstick on ≥2 occasions, or unexplained haematuria
- Abnormal urea & electrolytes defined as the values outside of normal ranges listed below
    - Potassium: 3.5-5.2 mmol/l
    - Sodium: 135-145 mEq/L
    - Creatinine (Adult men: ~0.7–1.3 mg/dL (62–115 µmol/L), Adult women: ~0.6–1.1 mg/dL (53–97 µmol/L))
    -
- Acute illness with RBS > 15 mmol/L
- Poor control on maximum tolerated oral agents
- Suspected kidney disease (physical symptoms indicative of kidney disease such as polyuria, edema)

*Note: If kidney disease is present or suspected, then CHEWs will be asked to consult a physician before initiating or continuing glibenclamide.*

**Outcomes**

Primary Effectiveness Outcome (Aim 3 )
- The **primary outcome** will be the difference the 6-month rolling average of the diabetes screening among eligible patients, defined as a random plasma glucose screening among adults with symptoms of hyperglycemia or a fasting plasma glucose among adults 18 years of age and body mass index $\geq$ 25 kg/m$^2$ in accordance with HEARTS-D, between the pre-implementation and implementation periods.

Primary Implementation Outcomes (Aim 3)
- Dose of quarterly supportive supervision visits measured by the proportion of observed/expected visits during the implementation period.

Secondary Effectiveness Outcomes (Aim 3)
- **Secondary outcomes** will compare the 6-month rolling average of diabetes treatment and control and mean fasting glucose levels in the pre-implementation and implementation periods.

Safety Outcomes (Aim 3)

**Safety outcomes** will include between-period (pre-implementation versus implementation) differences in rates of:

- Serious adverse events
- Adverse events of special interest (e.g., hypoglycemia, hyperglycemia, medication allergies, common medication side effects) in pre-implementation and implementation periods.

To improve safety monitoring, 5 PHCs with adequate staff and capacity for laboratory testing will be selected for routine collection of **urine, blood glucose, urea, creatinine, and electrolytes** for 100 patients (20 patients per PHC) starting or escalating therapy.

*We will assess for unanticipated problems to adhere to US federal regulations.

Definitions of Treatment and Control:

- Treatment will be defined by the prescription of any glucose lowering drug. Control will be defined according to the WHO HEARTS-D module[33] specifically: fasting glucose <126 mg/dl, postprandial glucose <160 mg/dl or HbA1c <7% (when available).

Sustainment of hypertensive services in the Federal Capital Territory. We will evaluate temporal trends of hypertension treatment and control during the study period in the 10 participating PHCs among patients with and without diabetes using District Health Information System - 2 (DHIS-2). We will assess for linear trends and will account for clustering among PHCs. We will then compare the trends in hypertension control with the other 50 PHCs in the Federal Capital Territory that previously implemented HEARTS during the initial funding period. At the recommendation of the Federal Ministry of Health, PHCs are now reporting data on vital signs and blood pressure lowering medications to DHIS-2 for centralized monitoring of hypertension service integration. We have already used an Application Programming Interface (API) from REDCap to demonstrate feasibility of de-identified data transfer to facilitate monitoring and evaluation. We have also received de-identified data from DHIS-2 through the Nigeria Hypertension Control Initiative for comparison with the HTN Program.

## 4. DATA AND SPECIMEN BANKING

No specimens will be banked as a part of this program.

Data will be collected at public, primary healthcare centers in the form of a hypertension treatment card for participants with hypertension and diabetes treatment cards for participants with diabetes. Patients will be administered a hypertension/diabetes card for their own use. Data from the site hypertension/diabetes treatment cards will be abstracted to REDCap by healthcare workers at the primary healthcare center or by the research team.

Data will be collected electronically in a REDCap database housed at University of Abuja. Only trained program staff or healthcare workers with University of Abuja approved access privileges will have access to the electronic database. We will restrict export rights to the program statisticians and database manager only. All exports will be housed in secure Washington University Box folder, or University of Abuja folder with restricted access. Washington University Box backs up data daily to prevent loss. Refer to the DSMP and DMP for details on data and safety monitoring and quality checks.

The HTN Program team will retain all program records required by applicable regulatory bodies in a secure and safe facility for a minimum period of seven years. Access to program records will be limited to program team members, unless through written application to and approval by the program Steering Committee.

## 5. SHARING RESULTS WITH PARTICIPANTS

During the program participants with hypertension will receive a hypertension treatment card upon which blood pressure information will be recorded at each visit. Participants with diabetes will receive a diabetes treatment card with blood glucose information recorded at each visit.

After completion of the program, to ensure that our results are used by researchers, policymakers, and community-based organizations, we will:

1. Make our research findings available at www.ClinicalTrials.gov (Identifier: pending), as required by US law.
2. Peer review all published products with the research team, study partners, and patient advocacy group.
3. Include local Nigerian investigators and community collaborators as authors.
4. Follow requirements of the sponsor, the National Heart, Lung, and Blood Institute of the NIH, to make all research papers made freely available to the public through PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/) at the time of publication with data available thereafter in accordance with NHLBI policy through NHLBI BioData Catalyst.
5. Make the study protocols and instruments available to other researchers through an open access journal and the University of Abuja website. Both English and French versions will be made available to allow for dissemination to French-speaking African countries, especially those in west Africa.
6. Report the results at conferences that target researchers, community health providers, and policymakers.
7. Hold a writing retreat to produce a Science to Community report that will be in English, Hausa, Igbo, and Yoruba.
8. Write health article and opinion editorials for local Nigerian newspapers.
9. Present our project to the Patient Advocacy Group for input and help with dissemination.
10. Make Science to Community report widely available throughout Nigeria.
11. Work with University of Abuja media department, the International Society of Media in Public Health, and Resolve to Save Lives to strategize methods for disseminating findings through Nigerian local and national television, radio, newspaper, and online outlets.
12. If the proposed health care and patient-level interventions show effectiveness, then we will develop an implementation manual, which can be disseminated throughout Nigeria as well as other countries.
13. The proposed dissemination plan will be evaluated as part of the implementation evaluation through completion of the proposed activities, number of individuals and organizations that participate in these activities, and resulting spread and scale of the system-, health worker-, and patient-level strategies.

## 6. PROGRAM TIMELINES

Patients will participate in the program from the time they registered until completion of the program. Patients will be continuously registered throughout the entire program, over 3 years of registration. The primary analysis will be completed within 12 months of program completion. Refer to the timeline below for details.

| | Pre-Award | Year 1 | | | | Year 2 | | | | Year 3 | | | | Year 4 | | | | Year 5 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4* |
| **Aim 1** | | | | | | | | | | | | | | | | | | | | | |
| Finalize, execute contracts/agreements | | | | | | | | | | | | | | | | | | | | | |
| Finalize, submit Aim 1 docs for IRB review | | | | | | | | | | | | | | | | | | | | | |
| Stakeholder engagement, Advis Board mtgs | | | | | | | | | | | | | | | | | | | | | |
| Collect quant./qual. formative data | | | | | | | | | | | | | | | | | | | | | |
| Analyze, report, and disseminate formative results for HEARTS adaptation | | | | | | | | | | | | | | | | | | | | | |
| Recruit, train 4 health care workers per site, 50 sites, 5 states (n=200) | | | | | Data collection | | | | | | HEARTS clinical | | | | | | | | | | |
| **Aim 2** | | | | | | | | | | | | | | | | | | | | | |
| Identify, assemble DSMB members | | | | | | | | | | | | | | | | | | | | | |
| Draft, finalize study documentation, including MOP, DMP, DSMB charter, SAP for Aims 2/3 | | | | | | | | | | | | | | | | | | | | | |
| Approval of DSMB charter, Aim 2/3 protocols | | | | | | | | | | | | | | | | | | | | | |
| Registration on clinicaltrials.gov (prior to 1st participant recruited) | | | | | | | | | | | | | | | | | | | | | |
| Pre-implementation data collection | | | | | | | | | | | | | | | | | | | | | |
| HEARTS implementation, including supportive supervision and drug revolving fund implementation in Abia, Delta, Gombe, Jigawa, Oyo | | | | | | | | | | | | | | | | | | | | | |
| Mid-term qualitative evaluation | | | | | | | | | | | | | | | | | | | | | |
| Endline mixed methods evaluation, including NoMAD, PSAT data collection | | | | | | | | | | | | | | | | | | | | | |
| Effectiveness/implement. outcome analyses | | | | | | | | | | | | | | | | | | | | | |
| Report, disseminate results of Aim 2 | | | | | | | | | | | | | | | | | | | | | |
| **Aim 3** | | | | | | | | | | | | | | | | | | | | | |
| Recruit, train 4 health care workers per site, 10 sites, 1 state (n=40) | | | | | Data collection | | | | | | HEARTS-D clinical | | | | | | | | | | |
| Pre-implementation data collection | | | | | | | | | | | | | | | | | | | | | |
| HEARTS-D implementation, including supportive supervision and drug revolving fund implementation in FCT | | | | | | | | | | | | | | | | | | | | | |
| Effectiveness/implement. outcome analyses | | | | | | | | | | | | | | | | | | | | | |
| Evaluate sustainment of hypertension care | | | | | | | | | | | | | | | | | | | | | |
| Collect process evaluation qualitative data | | | | | | | | | | | | | | | | | | | | | |
| Effectiveness/process evaluation analyses | | | | | | | | | | | | | | | | | | | | | |
| Report, disseminate results of Aim 3 | | | | | | | | | | | | | | | | | | | | | |

**Table.** Schedule of events (study timeline) by Aim. Gray boxes = activity period; Black boxes = milestones; *denotes buffer period.

## 7. INCLUSION AND EXCLUSION CRITERIA

Inclusion and Exclusion Criteria:

Patients diagnosed with hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg measured on two separate occasions or treated with a blood pressure lowering drug), according to 2019 Nigeria Hypertension Guidelines or with controlled (SBP <140 mm Hg and DBP <90 mm Hg) hypertension among those who are treated with blood pressure lowering drugs will be continuously registered. Patients will be registered upon the first diagnosis of hypertension or visit to the primary healthcare center during the registration period.

Aim 2 Inclusion criteria:

- Adults (≥18 years old),
- Elevated blood pressure (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) documented or measured by a health care professional (e.g., physician, CHEW, or community health officer) on two separate occasions or taking a BP-lowering medication, or a history of hypertension.
- Pregnant women are eligible for this program, or
- Cognitively impaired adults are eligible for this program.

This program will not include any of the following special populations:

- Individuals who are not yet adults (minors): i.e. infants, children, or teenagers <18 years old, or
- Prisoners or other detained individuals.

Aim 3 Inclusion Criteria:
Patients will be screened for diabetes with symptoms of hyperglycemia or BMI ≥25 kg/$m^2$ and over the age of 18 years old. Upon first or previous diagnosis, diabetes patients will be registered.

- Adults (≥18 years),
- Patients with previous diabetes diagnosis
- Patients with persistently elevated random glucose ≥200 mg/dl, fasting glucose ≥126 mg/dl, or hemoglobin A1c ≥6.5% on two or more occasions (when available)
- Patients taking glucose lowering medications
- Pregnant women are eligible for this program, or
- Cognitively impaired adults are eligible for this program.

This program will not include any of the following special populations:
- Individuals who are not yet adults (minors): i.e. infants, children, or teenagers <18 years old, or
- Prisoners or other detained individuals.

## 8. VULNERABLE POPULATIONS

Pregnant women and cognitively impaired adults are eligible for this program. This program included evidence-based treatment and standard of care based on the 2019 Nigeria hypertension guidelines. Pregnant women may be registered and treated per the 2019 Nigeria hypertension guidelines, which recommends referral for specialist management. Cognitively impaired individuals may be registered and treated per current and local hypertension guidelines. Pregnant women with diabetes will be included in the registry but will be referred for specialist management.

## 9. PARTICIPANT POPULATION(S)

Aim 2 Participants:

| Location | Category/Group: | Target Patient Visits |
|---|---|---|
| Abia | Adults | 12,600 patient visits |
| Delta | Adults | 12,600 patient visits |
| Gombe | Adults | 12,600 patient visits |
| Jigawa | Adults | 12,600 patient visits |
| Oyo | Adults | 12,600 patient visits |
| Total: | | 63,000 patient visits |

Aim 3 Participants:

| Location | Category/Group: | Target Patient Visits |
|---|---|---|
| Federal Capital Territory (FCT) | Adults | 18,000 patient visits |

| | | |
|---|---|---|
| Total: | | 18,000 patient visits |

## 10. RECRUITMENT METHODS

A community awareness campaign for hypertension will be conducted in the 5 new states and a community awareness campaign for diabetes will be conducted in the Federal Capital Territory. Participants will not be recruited but will be continuously registered upon initial diagnosis of hypertension or diabetes or first presentation at a participating primary healthcare center with pre-existing controlled or uncontrolled hypertension or diabetes. For WHO HEARTS participants will be registered at 50 primary healthcare centers across 5 states, for WHO HEARTS-D participants will be registered at 10 primary healthcare centers across the Federal Capital Territory.

## 11. COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participants will not be compensated for participation in this program.

## 12. WITHDRAWAL OF PARTICIPANTS

If the treating health worker, study team, or DSMB deems it unsafe for any participant to continue any program procedures, then he / she may withdraw the participant. If a participant is incarcerated, becomes terminally ill, or experiences any other circumstance that would make continued involvement in the program unfeasible or unethical, then the HTN Program team may withdraw the participant. In all cases, any data already collected will not be removed from the program database and may still be used in analyses unless explicitly requested by the participant.

## 13. RISKS TO PARTICIPANTS

During this program, participants will be prescribed blood pressure and glucose lowering medications, it is possible that participants may experience adverse effects from these medications. These risks are considered no more than minimal in the course of routine clinical care, provided that health workers have sufficient training, supervision, and monitoring.

## 14. POTENTIAL BENEFITS TO PARTICIPANTS

During this program, participants may be prescribed blood pressure lowering medications, which may help control their blood pressure and lower their risk for cardiovascular related events during this period. Participants may be prescribed blood glucose lowering medications, which may help control their blood glucose levels and lower their risk for adverse health effects due to high blood glucose levels during this period.

## 15. DATA MANAGEMENT AND CONFIDENTIALITY

Data Management

Electronic data will be stored in the eCRFs maintained using the University of Abuja REDCap platform. Thus, only trained study team members with appropriate credentials and passwords will have ability to enter and view program data. Export rights will be restricted to the program statisticians only, and de-identified data will only be exported when necessary for reporting and quality control purposes to a restricted Washington University Box folder or to a restricted location at University of Abuja.

To ensure data quality, we will build in field validation(s) and branching logic within the forms, use a first / second pass data entry workflow, and we will use the field comment logs and data resolution workflow module within REDCap. Before obtaining data entry rights in production, program team members must complete a training and pilot test entry of hypothetical data. We will document these training sessions and successful completion of any program data entry practicums.

Further, we will perform centralized monitoring through Data and Status Quality Reports (DSQRs) and REDCap reporting features. The DSQRs will use the REDCap application programming interface (API) functionality to export the program data and then restructure and summarize the data using statistical software, such as R or SAS. The output for these DSQRs will be housed on Washington University Box folder or University of Abuja's secure servers with restricted access to program team members only. The reports will be reviewed and discussed bi-weekly, on average, but once the systems are in place and code generated, the reports may be updated in real-time.

The contents of these reports may continually evolve throughout the course of the program, but they will focus on the following essential program data:

- Baseline and follow-up information – registration, demographics, clinical history, treatment and control, drug classes and number baseline and follow-up SBP, DBP, glucose, and hemoglobin A1c,
- Primary and secondary response variables
- SAEs and AEs of special interest

For the purposes of these reports, we will present data in aggregate form overall and by program site. In addition to these general data summarizations, we plan to employ statistical methods for monitoring clinical trial data.[16]The general strategies include:

- Exploration of:
    - Descriptive statistic summaries overall and by site for essential program data as indicated above.
    - Frequency of outlying values overall and by site.
    - Process measures overall and by site:
        - Outlier and inlier rates
        - Blood pressure measurement digit preference (0, 5, even numbers)
        - Blood glucose digit preference (whole number-mg/dL)
        - Correlation coefficients of key covariates
        - Deviations, SAEs, and AEs of special interest by site
        - Timeliness of data entry
        - Proportion of dropouts / losses to follow-up
- Evaluating important response and safety data univariately and also longitudinal trajectories over time (within the same person).
- Multivariate techniques involving principal components (PC1 vs. PC2) and examining multivariate outliers. For example, we may examine mean for individual center vs. that of all other centers. Plot PCs for p-values for all variables and identify outliers (those outside of the central cloud).
- Tests on randomness – Benford's law on the distribution of digits.

Statistical Design and Sample Size

The statistical design of the program intervention includes evaluation of effectiveness and implementation co-primary outcomes. For effectiveness outcomes, we will use an interrupted time series design with analysis plans and power calculations outlined in the Statistical Analysis Plan, which use conservative baseline treatment and control estimates, effect sizes, and temporal trend rates to minimize the risk of being underpowered to detect a potential difference while operating within a feasible project size, timeline, and budget. For implementation outcomes, we will use mixed methods analysis using the RE-AIM framework to triangulate both routinely collected quantitative data and qualitative data to evaluate the reach, secondary effectiveness, adoption, implementation, and maintenance, acceptability, and cost of the implementation bundle for Aims 2 and 3.

We will evaluate change in temporal trends for primary and secondary outcomes through segmented linear regression, aggregating data across primary health care centers by month (centered to time=0 when intervention is implemented). To evaluate the individual effects of bundle components and time variance in implementation on our primary outcomes, we will use patient-level mixed effects models including random effects to account for clustering at the primary healthcare center level. We will perform sensitivity analyses by both excluding and restricting repeated measures of the same patients over the program period.

Please refer to the Statistical Analysis Plan for additional details on statistical design and power.

## 16. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

The DSMP documents the provisions to monitor the data and ensure safety of all program participants. Briefly, (1) we have convened an independent DSMB consisting of five members with diverse backgrounds and fields of expertise; (2) the DSMB will meet at minimum every 6-12 months to review safety and essential program data; (3) we will employ centralized statistical monitoring approaches as mentioned above and in the SAP to monitor data quality and safety; and (4) we plan for targeted on-site monitoring by research staff through supported supervision.

## 17. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS

Information regarding patient privacy relevant to data and specimens is described within this protocol in section Data and Specimen Banking.

## 18. COMPENSATION FOR RESEARCH-RELATED INJURY

This program is investigator-initiated. If participants become ill or are injured as a result of this program (medications, devices or procedures), then they will be directed to seek medical treatment through their doctor or treatment center of choice and to promptly tell the program doctor or health worker about any illness or injury. The researchers and clinical staff will not pay for medical care required because of a bad outcome resulting from participation in this program.

## 19. ECONOMIC BURDEN TO PARTICIPANTS

We do not anticipate that patients will experience economic burdens related to participation in this program. Evaluation and treatment of hypertension will be performed according to clinical practice guidelines.

## 20. CONSENT PROCESS

Participants will not be consented for this system-level intervention based on standard of care. A waiver of consent for the HTN Program will be sought from the Federal Capital Territory Health Research Ethics Committee and University of Abuja Teaching Hospital Ethics Board, and the Washington University in St. Louis Institutional Review Board.

## 21. NON-ENGLISH-SPEAKING PARTICIPANTS

We anticipate registering Yoruba-, Igbo-, Hausa-, and English-speaking participants in this HTN Program. Participant facing materials are designed for comprehension by non-literate and non-English speaking individuals.

## 22. WAIVER OR ALTERATION OF CONSENT PROCESS

Participants will not be consented for this system-level intervention that seeks to strengthen the current standard of care. A waiver of consent for the HTN Program will be sought from the Federal Capital Territory Health Research Ethics Committee, University of Abuja Teaching Hospital Ethics Board, and the Washington University in St. Louis Institutional Review Board.

## 23. PROTECTED HEALTH INFORMATION (PHI AND HIPAA)

This program is conducted in Nigeria, where HIPAA does not apply. Information regarding patient privacy relevant to data and specimens is described within this protocol in section Data and Specimen Banking.

## 24. QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The University of Abuja is 1 of the 40 Federal Government owned universities in Nigeria. It is in the Federal Capital of Nigeria and was established in 1988 as a dual-mode university with the mandate to run conventional and distance learning programs. The University of Abuja encourages and promotes scholarship and the conduct research in all fields of learning and human endeavor which is related to the social, cultural and economic needs of the people of Nigeria. The University of Abuja works in collaboration her sister institution, the University of Abuja Teaching Hospital for the training of medical students and conduct of medical research. The University of Abuja Teaching Hospital campus houses the Cardiovascular Research Unit which is involved in conducting and coordinating different types of cardiovascular including community-based studies, large observational hospital- based studies which are either cohort or longitudinal randomized controlled trials and national and international collaborative research work. The University has an Information Communication Technology (ICT) Center that is well equipped to provide computing facilities to support teaching, research, consultancy and administrative activities for all Units in the University. The center has appropriate modern hardware and software as well as highly skilled personnel and has the responsibility of developing a robust ICT infrastructure and corresponding services to facilitate the teaching, learning, research and administrative functions of the University. Research staff at the University of Abuja and University of Abuja Teaching Hospital will oversee all aspects of this program.

## 25. MULTI-SITE RESEARCH

Drs. Ojji and Huffman will co-lead the overall oversight, management, and coordination of the proposed program as the co-principal investigators. Dr. Ojji will oversee personnel and staff recruitment and management in Abuja. Chidubem Okoli will serve as the Nigeria project manager and will be responsible for day-to-day management of the proposed research activities with support from research nurses, Ms. Glory Hansen and Regina Asuku, data quality officer Ms. Confidence Alo-Joseph, and data entry staff, Ms. Charity Akor. Dr. Charles Goss will serve as lead biostatistician. Drs. Ming Cheng and Mansi Agarwal will serve as a program biostatisticians. Dr. Julia López will be responsible for assisting in qualitative data collection and analysis with support from Dr. Hirschhorn and oversight by Drs. Huffman and Ojji. Ms. Valerie Graham will be the US project manager.

The research team will communicate in weekly operations team meetings and at least quarterly with the program sponsor. The REDCap electronic data capture system will serve as a bi-directional communication platform for our primary healthcare centers. We will also create and utilize an email listserv to send out quarterly newsletters of our progress.

All required approvals (initial, continuing review and modifications) will be obtained from the Federal Capital Territory Health Research Ethics Committee, University of Abuja Teaching Hospital Health Research Ethics Committee, and Washington University IRB. All modifications will be communicated to sites, and approved, including approval by the IRB of record, before the modification is implemented. All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies. All local site investigators will conduct the program in accordance with applicable federal regulations and local laws. All non-compliance with the program protocol or applicable requirements will be reported in accordance with local policy.

**TABLE 1: IMPLEMENTATION OUTCOMES TABLE (**Definitions for Implementation Outcomes at Program, Center, and Individual Levels)

| | Level | Outcome | Method of calculation | Data source | Timing |
|---|---|---|---|---|---|
| **REACH** | Program (aim 2) | Number of participating PHCs/total number of PHCs in all participating states | A = Number of participating PHCs<br>B = Total number of PHCs in all participating states<br>Calculation: A ÷ B | Registry data | Baseline |
| | Program (aim 3) | Number of PHC's participating in the FCT/ total number of PHCs in HTN 1.0 | A: Number of participating PHCs in the FCT<br>B: Total number of PHCs in HTN 1.0 (60)<br>Calculation: A ÷ B | Registry data | Baseline |
| | Center (aim 2) | Diversity of participating PHCs and staff in terms of size, ward, baseline staffing levels | PHCs' size = Number of patients; Number of visits<br><br>Diversity of PHCs in terms of ward = Number of PHCs in each area council<br><br>Diversity of staff = Number of staff in each area council at the baseline supervision visit | Registry data, supervision data | Baseline to study end |
| | Center (aim 3) | Diversity of participating PHCs and staff in terms of size, ward, baseline staffing levels | PHCs' size = Number of patients; Number of visits<br><br>Diversity of PHCs in terms of ward = Number of PHCs in each area council<br><br>Diversity of staff = Number of staff in each area council at the baseline supervision visit | Registry data, supervision data | |
| | Individual (aim 2) | Number of adult patients with BPs measured / total number of | Total number of adult patient visits to the health facility within the given dates | Supervision data | |

| | | | | | |
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| | | adult patients within participating PHCs within the given dates | documented at the first and last supervision visits, N<br><br>Of these adult patients, how many had their BP checked during their visit? N (%)<br><br>Of the patients who had their BP checked, how many had high BP? Median N (%) | | |
| **EFFECTIVENESS** | Program (aim 2) | Hypertension control within the overall system of participating PHCs between the pre-implementation and implementation periods, defined by 6-month rolling average (defined as <140/90 mm Hg) | 6-month rolling average control rate (<140<90) for all PHCs | Registry data | Baseline to study end |
| | Program (aim 2) | Hypertension control within the overall system of participating PHCs for the implementation period, defined by 6-month rolling average (defined as <130/80 mm Hg) | 6-month rolling average hypertension control rate (<130/80 mm Hg) for all PHCs | Registry data | |
| | Program (aim 2) | Mean SBP and DBP within the overall system of participating PHCs for the implementation period, defined by 6-month | 6-month rolling average SBP for all PHCs<br><br>6-month rolling average DBP for all PHCs | Registry data | |

| | | | | | |
|---|---|---|---|---|---|
| | | rolling average and based on last visit | Last visit's SBP for all PHCs<br><br>Last visit's DBP for all PHCs | | |
| | Center (aim 2) | Control rates across participating PHCs for the implementation period, defined by 6-month rolling average | 6-month rolling average control rate | Registry data | |
| | Center (aim 2) | Mean SBP and DBP across participating PHCs for the implementation period, defined by 6-month rolling average and based on last visit | 6-month rolling average SBP<br><br>6-month rolling average DBP<br><br>Last visit's SBP<br><br>Last visit's DBP | Registry data | |
| | Program (aim 3) | **Secondary outcomes** will compare the 6-month rolling average of diabetes treatment and control and mean fasting glucose levels in the pre-implementation and implementation periods.<br>**2º effectiveness outcome** | 6-month rolling average diabates treatment and control in the implementation period compared with the pre-implementation period | Registry data | Baseline to study end |
| | Program (aim 3) | The **primary outcome** will be the difference in the 6-month rolling average of the diabetes screening among eligible | Total number of adult patient visits to the health facility within the given dates documented at the first and last supervision visits, N | Supervision data | Baseline to end |

| | | | | | |
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| | | patients, defined as a random plasma glucose screening among adults with symptoms of hyperglycemia or a fasting plasma glucose or hemoglobin A1c testing (when available) among adults ≥ 18 years old and body mass index ≥ 25 kg/m$^2$ in accordance with HEARTS-D, between the pre-implementation and implementation periods.<br>**1° effectiveness outcome** | Of the eligible adult patients (i.e., those with symptoms of hyperglycemia or meeting screening criteria), how many had their glucose or hemoglobin A1c checked during their visit? N (%)<br><br>Of the eligible patients who had their glucose checked, how many had elevated glucose (fasting or random) or elevated hemoglobin A1c? Median N (%) | | |
| **ADOPTION** | Program (aim 2) | Percentage of patients treated with fixed dose combination therapies in the last 6 months | A = Number of patients in HTN 2.0 Program that were treated with fixed dose combination therapies in the last 6 months.<br>B = Total number of patients in HTN 2.0 Program<br><br>Calculation: A ÷ B | Registry data | Baseline to study end |
| | Program (aim 3) | Percentage of patients treated with glucose lowering drugs in the last 3-months | A = Number of patients in the FCT in the HTN 2.0 Program aim 3 that were treated with glucose lowering drugs in the last 3 months.<br>B = Total number of patients in the FCT in | Registry Data | Baseline to study end |

| | | | | | |
|---|---|---|---|---|---|
| | | | the HTN 2.0 Program aim 3<br><br>Calculation: A ÷ B | | |
| **IMPLEMENTATION** | Program (aim 2) | Proportion of observed site supervision visits to expected visits<br><br>**1° implementation outcome** | A = Number of supportive supervision visits<br>B = Expected number of quarterly supportive supervision visits<br><br>Calculation: A ÷ B | Supervision data | Baseline to study end |
| | Program (aim 3) | Proportion of observed site supervision visits to expected visits<br><br>**1° implementation outcome** | A = Number of supportive supervision visits<br>B = Expected number of quarterly supportive supervision visits<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 2) | Proportion of selected PHCs who participated in baseline hypertension training | A = Number of PHCs who participated in baseline hypertension training<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 3) | Proportion of selected PHCs who participated in baseline diabetes training | A = Number of PHCs who participated in baseline diabetes training<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 2) | Proportion of selected PHCs who participated in site initiation training | A = Number of PHCs who participated in site initiation training<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |

| | | | | | |
|---|---|---|---|---|---|
| | Program (aim 2) | Proportion of selected PHCs who received at least one supportive supervision visit in the past 12 months | A = Number of PHCs who received at least one supportive supervision visit in the past 12 months<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 3) | Proportion of selected PHCs who received at least one supportive supervision visit in the past 12 months | A = Number of PHCs who received at least one supportive supervision visit in the past 12 months<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 2) | Proportion of selected PHCs who received an audit and feedback report within the past 3-months | A = Number of PHCs who received at least an audit and feedback report within the past 3-months<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 3) | Proportion of eligible PHCs who received an audit and feedback report within the past 3-months | A = Number of PHCs who received at least an audit and feedback report within the past 3-months<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 2) | Percentage of PHCs with a working blood pressure monitor at the site on the day of assessment | A = Number of PHCs with a working blood pressure monitor at the site on the day of assessment (time point: last supervision visit)<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |

| | | | | | |
|---|---|---|---|---|---|
| | Program (aim 3) | Percentage of PHCs with a working blood glucose monitor at the site on the day of assessment | A = Number of PHCs with a working blood glucose monitor at the site on the day of assessment (time point: last supervision visit)<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 2) | Percentage of PHCs with blood pressure medicines available on the day of assessment | A = Number of PHCs with blood pressure medicines available on the day of assessment (time point: last supervision visit)<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 3) | Percentage of PHCs with diabetes medicines available on the day of assessment | A = Number of PHCs with diabetes medicines available on the day of assessment (time point: last supervision visit)<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B | Supervision data | |
| | Program (aim 2) | Percentage of patients with step up indicated who received step up treatment in the last 6-months | A = Number of patients who need step up treatment and received it<br><br>B = Total number of patients who are registered per month<br><br>Calculation: A ÷ B, 6-monthly rolling average rate | Registry data | |
| | Program (aim 3) | Percentage of patients with step up indicated who received step up treatment in the last 6-months | A = Number of patients who need step up treatment and received it | Registry data | |

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| | | | B = Total number of patients who are registered per month<br><br>Calculation: A ÷ B, 6-monthly rolling average rate | | |
| | Center (aim 2) | Number and proportion of adult patients with hypertension who are registered/total number of adult patients with elevated blood pressure within participating PHCs within the past 3 working days | A = Total number of adult patients who had high BP visits to the health facility within the given dates<br><br>B = Total number of patients visits to the health facility within the given dates<br><br>Calculation: A ÷ B | Supervision data | |
| | Center (aim 2) | Monthly proportion of registered patients with appropriate stepped care/total number of registered patients | A = Number of patients who need step up treatment and received it<br><br>B = Total number of patients who are registered per month<br><br>Calculation: A ÷ B, 6-monthly rolling average rate | Registry data | |
| | Center (aim 3) | Monthly proportion of registered patients with appropriate stepped care/total number of registered patients | A = Number of patients who need step up treatment and received it<br><br>B = Total number of patients who are registered per month<br><br>Calculation: A ÷ B, 6-monthly rolling average rate | Registry data | |

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| | Center (aim 2) | Monthly proportion of registered patients treated with fixed dose combination therapy/total number of patients on treatment | A = Number of patients who are treated with fixed dose combination therapy<br><br>B = Total number of patients who are treated per month<br><br>Calculation: A ÷ B, 6-month rolling average rate | Registry data | |
| **MAINTENANCE** | Program (aim 2) | Proportion of participating PHCs who maintain hypertension control above baseline at 12 and 24 months | A = Number of PHCs who maintain hypertension control above baseline rates at 12, and 24 months after implementation<br>B = Total number of selected PHCs<br><br>Calculation: A+B | Registry data | Baseline to study end |
| | Program (aim 2) | Proportion of participating PHCs without blood pressure medication stockouts at each quarter | A = Number of PHCs without blood pressure medication stockouts<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B = 0 | Supervision data | |
| | Program (aim 3) | Proportion of participating PHC's without glucose lowering medication stockouts at each quarter | A = Number of PHCs without glucose lowering medication stockouts<br>B = Total number of selected PHCs<br><br>Calculation: A ÷ B = 0 | Supervision data | |
| | Program (aim 3) | Proportion of aim 3 participating PHCs who maintain glucose control above baseline at 12 and 24 months | A = Number of PHCs who maintain glucose control above baseline at 12, and 24 months after implementation<br>B = Total number of PHCs in aim 3<br><br>Calculation: A+B | Registry Data | |

**TABLE 2: PROTOCOL AMENDMENT HISTORY**

| Version | Date | Description of Change | Brief Rationale |
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