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Integration of Hypertension Management into HIV Care in Nigeria: A Task Strengthening Strategy
RESEARCH PROTOCOL

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

CONTENTS

List of Abbreviations

AE	Adverse Events
BP	Blood Pressure
CFIR	Consolidated Framework for Implementation Research
CVD	Cardiovascular Disease
HAART	Highly Active Antiretroviral
HTN	Hypertension
ICF	Informed Consent Form
ICR	Identifying, Counselling and Referring
LSACA	Lagos State AIDs Council Agency
LSPHB	Lagos State Primary Healthcare Board
MOH	Ministry of Health
NCD	Non Communicable Disease
NIMR	Nigerian Institute of Medical Research
PF	Practice Facilitation
PHC	Primary Healthcare Center
PWH	People Living with HIV
RE-AIM	Reach Effectiveness Adoption Implementation Maintenance
REDCap	Research Electronic Data Capture
TASSH	Task Strengthening Strategy for Hypertension Control
TTT	Train the Trainer

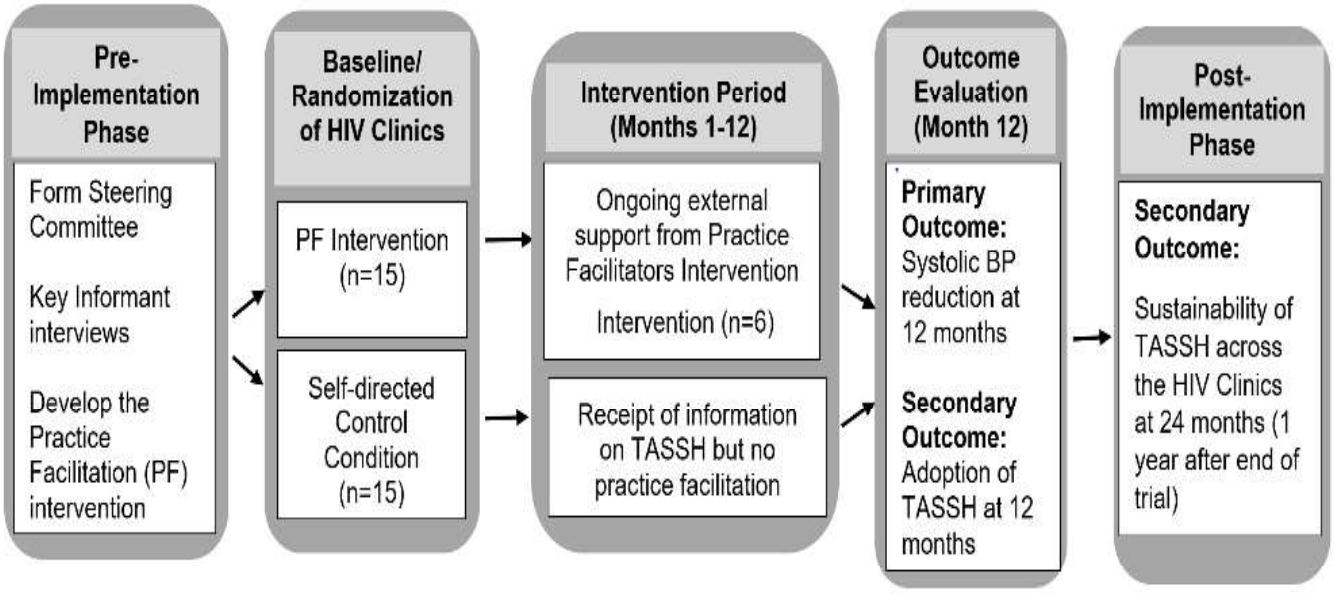
Protocol Summary

Title	Integration of Hypertension Management into HIV Care in Nigeria: A Task Strengthening Strategy
Short Title	Integration of Hypertension Management into HIV Care in Nigeria: A Task Strengthening Strategy
Brief Summary	The study will be conducted in 3 phases: 1) a pre-implementation phase that will use CFIR to develop a tailored PF intervention for integrating TASSH into HIV clinics; 2) an implementation phase that will use RE-AIM to compare the clinical effectiveness of PF vs. a self-directed condition (receipt of information on TASSH without PF) on BP reduction; and 3) a post- implementation phase that will use RE-AIM to evaluate the effect of PF vs. self-directed condition on adoption and sustainability of TASSH. The PF intervention components comprises: (a) an advisory board to provide leadership support for implementing TASSH in PHCs; (b) training of the HIV nurses on TASSH protocol; and (c) training of practice facilitators, who will serve as coaches, provide support, and performance feedback to the HIV nurses.
Phase	Late stage phase 4 clinical trial
Objectives	**Aim 1:** Identify the capacity (barriers and facilitators) of the PHCs to adapt TASSH and develop a context- specific PF intervention for its implementation using qualitative methods guided by CFIR. **Aim 2:** Compare in a cluster RCT of 30 PHCs, the effect of PF intervention versus self-directed condition on systolic BP reduction among 960 HIV patients with HTN (BP>140/90 mmHg). **Aim 3:** Compare in a cluster RCT of 30 PHCs, effect of the PF intervention versus self-directed condition on TASSH adoption and sustainability **Aim 4:** Determine the mediators of adoption and sustainability of TASSH across the 30 PHCs at 12 months and 24 months.
Methodology	Training of the HIV clinic nurses on the TASSH protocol for BP measurement, CV assessment, initiation of treatment with antihypertensive medications, and referral of complicated cases. Specifically, HIV nurses at the PHCs will be trained on the components of the TASSH protocol based on the following steps: 1. Identify HIV patients with uncontrolled hypertension: trained HIV nurses will take patients' medical history (whether or not they have a diagnosis of diabetes, heart attack, stroke, heart failure, and smoking). 2. Next, they will measure the patients' weight, height, waist circumference and BP with a valid automated device following standard procedures. 3. Initiate lifestyle counseling and medication treatment every 1-3 months: The nurses will next counsel eligible patients on lifestyle behaviors for 20 to 30 minutes (increased intake of fruits and vegetables, moderate physical activity and reduce salt intake). 4. Refer patients with complicated HTN to physicians for further care.
Endpoint	The primary outcome is change in systolic blood pressure (BP) from baseline to 12 months. Secondary outcomes are:

	1. Rate of adoption [proportion of PHCs that adopted TASSH at 12 months] and sustainability [maintenance of the uptake of TASSH at 24 months, one year after completion of the trial]. Adoption will be based on a composite measure of adoption ratings to assess the degree to which the three essential elements of the TASSH protocol (identification and screening of patients for HTN; proportion of patients who received lifestyle counseling by the HIV clinic nurses; and proportion of HTN patients referred for initiation of antihypertensive medication treatment). 2. The mediators of adoption and sustainability of TASSH across the primary health centers (PHCs) at 12 and 24 months.
Study Duration	24 months
Participant Duration	12 months
Population	HIV patients with uncontrolled hypertension who are 18 years and older attending one of the 30 PHCs.
Study Sites	30 Primary Healthcare Centers
Number of Participants	960 HIV+ patients with uncontrolled HTN
Description of Study Agent/ Procedure	Practice Facilitation
Reference Therapy	TASSH but no practice facilitation
Key Procedures	Ongoing external support from Practice Facilitators Intervention
Statistical Analysis	Analysis for Aim 1: Qualitative Data Analysis for the Pre-Implementation Phase Analysis for Aim 2 will consist of a repeated measures mixed-effects model for systolic BP (SBP), with fixed effects for time and intervention arm, and random effects for clinic. Analysis for Aim 3: The qualitative components of sustainability at 24 months will be assessed using interviews with nurses and clinic leadership. These interviews will be recorded, transcribed and entered into NVIVO Version 11 for analysis.

Schematic of Study Design

Figure 1. Study Design



Section 1: Summary of the Study

Study description: Guided by the Consolidated Framework for Implementation Research (CFIR) and the Reach Effectiveness Adoption Implementation and Maintenance (RE-AIM) framework, this study will evaluate, in a hybrid clinical effectiveness-implementation design, the effect of a replicable practice facilitation (PF) strategy to implement an evidence-based Task-Strengthening Strategy for Hypertension control (TASSH) as an integrated model for people living with HIV (PWH) across 30 primary healthcare centers (PHCs) in Lagos, Nigeria. The study will be conducted in 3 phases: 1) a pre-implementation phase that will use CFIR to develop a tailored PF intervention for integrating TASSH into HIV clinics; 2) an implementation phase that will use RE-AIM to compare the clinical effectiveness of PF vs. a self-directed condition (receipt of information on TASSH without PF) on BP reduction; and 3) a post- implementation phase that will use RE-AIM to evaluate the effect of PF vs. self-directed condition on adoption and sustainability of TASSH. The PF intervention components comprises: (a) an advisory board to provide leadership support for implementing TASSH in PHCs; (b) training of the HIV nurses on TASSH protocol; and (c) training of practice facilitators, who will serve as coaches, provide support, and performance feedback to the HIV nurses.

Objectives

- **Aim 1:** Identify the capacity (barriers and facilitators) of the PHCs to adapt TASSH and develop a context- specific PF intervention for its implementation using qualitative methods guided by CFIR.
- **Aim 2:** Compare in a cluster RCT of 30 PHCs, the effect of PF intervention versus self-directed condition on systolic BP reduction among 960 HIV patients with HTN (BP>140/90 mmHg).
- **Aim 3:** Compare in a cluster RCT of 30 PHCs, effect of the PF intervention versus self-directed condition on TASSH adoption and sustainability
- **Aim 4:** Determine the mediators of adoption and sustainability of TASSH across the 30 PHCs at 12 months and 24 months.

Endpoints

3. The primary outcome is change in systolic blood pressure (BP) from baseline to 12 months.
4. Secondary outcomes are:
    a. Rate of adoption [proportion of PHCs that adopted TASSH at 12 months] and sustainability [maintenance of the uptake of TASSH at 24 months, one year after completion of the trial]. Adoption will be based on a composite measure of adoption ratings to assess the degree to which the three essential elements of the TASSH protocol (identification and screening of patients for HTN; proportion of patients who received lifestyle counseling by the HIV clinic nurses; and proportion of HTN patients referred for initiation of antihypertensive medication treatment).
    b. The mediators of adoption and sustainability of TASSH across the primary health centers (PHCs) at 12 and 24 months.

Study population: HIV patients with uncontrolled hypertension who are 18 years and older attending one of the 30 PHCs.

Phase: This is a late stage phase 4 clinical trial.

Description of Site/ Facilities Enrolling Participants: The study takes place in 30 primary healthcare centers in Lagos, Nigeria. As a leading research institution in Nigeria with established excellence in operational research for health promotion and disease prevention, the Nigerian Institute of Medical

Research (NIMR) will serve as the Research Coordinating Center, and oversee all activities for the study. NIMR has successfully contributed to improving healthcare delivery for PWH in Nigeria through the implementation of evidence-based practices funded by PEPFAR and the Nigerian government. NIMR has long-standing relationship with the Lagos State AIDS Council Agency (LSACA) with which it works to provide HIV services. In addition, NIMR's Center for HIV/AIDS Treatment has the largest database of PWH in Nigeria with over 20,000 clients.

Description of Study Intervention

The practice facilitation intervention has three components:

1) Formation of an advisory board of key stakeholders at all levels of care. The board will provide leadership support for the adaptation and integration of TASSH into PHCs.
2) Use of a Train-The-Trainer (TTT) model to train a cadre of experienced nurses from the Lagos State Primary Health Care Board, Directorate of Nursing to serve as practice outreach facilitators (POFs). The PF strategy includes: training of the POFs on coaching strategies (Engaging, Enhancing, & Evaluation) to help the HIV nurses perform their tasks; training the HIV nurses on Identifying, Counseling and Referring (ICR) of HIV patients with uncontrolled HTN to the health centers using the 5 As counseling strategy (ask, assess, advise, assist and arrange); and creation of a community learning environment that will support learning opportunities for the HIV nurses and POFs.
3) Training of the HIV clinic nurses on the TASSH protocol for BP measurement, CV assessment, initiation of treatment with antihypertensive medications, and referral of complicated cases. Specifically, HIV nurses at the PHCs will be trained on the components of the TASSH protocol based on the following steps:
    1. Identify HIV patients with uncontrolled hypertension: trained HIV nurses will take patients' medical history (whether or not they have a diagnosis of diabetes, heart attack, stroke, heart failure, and smoking).
    2. Next, they will measure the patients' weight, height, waist circumference and BP with a valid automated device following standard procedures.
    3. Initiate lifestyle counseling and medication treatment every 1-3 months: The nurses will next counsel eligible patients on lifestyle behaviors for 20 to 30 minutes (increased intake of fruits and vegetables, moderate physical activity and reduce salt intake).
    4. Refer patients with complicated HTN to physicians for further care.

SECTION 2: Introduction/ Background Information (citing relevant criteria)

Study rationale

Despite significant advances in HIV treatment, Africa still accounts for 70% of global burden of HIV.[1] Current estimates show that about two-thirds of HIV infections in West Africa and Central Africa occurred in Nigeria.[3] More importantly, access to highly active antiretroviral treatment (HAART) has led to increased survival of people living with HIV (PWH) in Africa. As such PWH are now at increased risk for non-communicable diseases (NCDs),[4] including cardiovascular diseases (CVD), diabetes and stroke,[5] with hypertension (HTN) as the most common.[6] Compared to the general population, PWH have higher CVD mortality,[3, 10] due to the increased burden of HTN.[11] For example, based on Global Burden of Disease, Nigeria had 95% increased mortality from 1990 to 2015 in adults with uncontrolled HTN.[12] There is thus, an urgent need for strategies to reduce the burden of HTN in PWH in Nigeria, especially those aimed at the efficient use of available resources. If the increased CVD-mortality in PWH is not addressed, there will

potentially be a reversal of the gains made in staving off the HIV epidemic in Africa as comorbidity of NCDs may complicate HIV treatment and management with resultant worsening of health outcomes.[13, 14]

Given the successful rollout of HIV care programs in Africa, there is growing consensus that integration of NCD management into HIV chronic care platforms may be a cost-effective for mitigating the rising burden of NCDs in PLWH.[4, 14] Although the need for integrated HIV/NCD care is recognized, evidence supporting context-specific strategies in Africa is limited.[13] In Nigeria, and despite the availability of evidence-based interventions for HTN control, the shortage of healthcare workers is a major barrier to HTN control where in 2015 there were 20 health workers per 10,000 population.[16] The acute shortage of physicians limits Nigeria's capacity to control HTN in PLWH at the basic primary care level such as the HIV clinics, where majority receive their care. In order to address this issue, the Nigerian Ministry of Health (MOH) developed a task shifting policy to be implemented at national and regional levels of its healthcare system.[17] Although the "Task-shifting and Task-sharing Policy for Essential Health Care Services in Nigeria" has been in place since 2014,[17] there is no evidence of its implementation as a strategy to integrate NCD management into HIV care platform.

As the most populous state in Nigeria with a population of 22 million, Lagos State adopts primary healthcare as the major hub of its healthcare delivery system. The Lagos State Primary Healthcare Board (LSPHB) manages about 100 community health centers with over 67 primary healthcare centers (PHCs). With a focus on community health and strengthening of human resources for integrated health services, LSPHB works with Lagos State AIDS Council Agency (LSACA) and the Nigerian Institute of Medical research (NIMR), to provide comprehensive HIV care across its 67 PHCs. Although NIMR instituted effective strategies for PWH across Lagos State, integration of evidence-based interventions like TASSH within HIV clinics remains untested. LSPHB's well-established network of HIV clinics in addition to NIMR's effective HIV care provides a unique opportunity for us to evaluate the integration of TASSH into care of PWH and comorbid HTN. Furthermore, the ubiquity of PHCs across Lagos State and their use as a platform for primary care delivery allows us to evaluate the adoption and sustainability of an integrated HIV/NCD model for HTN control in low-resource healthcare settings.

Risk/ Benefit Assessment

Known Potential Risks: To our knowledge, the proposed study does not pose any risk to study participants other than the following minor risks: A) Collection of personal and sensitive information, which may be requested during the course of the study. Patients do not have to answer any questions they choose not to. However, patients may be slightly inconvenienced as they have to provide dedicated time for the study visits and meetings with HIV nurses; and B) Because patients' blood pressure recordings and survey responses will be used as a source of data for this study, there is a potential risk of violation of their privacy. However, the research team is taking many steps to ensure that participants' private information is safely kept in a locked space, available only to authorized study staff.

Known Potential Benefits: Potential benefits for study participants include: a) potential reduction in blood pressure, improved cardiovascular risk profile and increased knowledge in management of HTN. B) HIV nurses will receive training that will boost their knowledge, confidence, competence and skills in management of HTN for patients with HIV.

Assessment of Potential Risks and Benefits: Potential risks and benefits will be assessed at each study visit (Baseline, 6, 12, 24 months). Detailed assessment of risks and benefits is listed under Study Assessment and Procedures.

SECTION 3: Study Objectives

Primary objective, endpoint, and justification

The primary objective is to compare in a cluster RCT of 30 HIV clinics, the effect of PF intervention versus a self-directed condition (receipt of information for implementation of TASSH but no facilitation) on systolic BP reduction among 960 HIV patients with HTN (BP>140/90 mmHg).

The primary outcome is change in systolic BP (SBP) from baseline to 12 months. Following existing TASSH protocol, the SBP reduction in patients will be assessed as mean change in systolic BP from baseline to 12 months. Blood pressure will be taken with valid automated BP device as follows:
At baseline, three BP readings will be taken by trained research coordinators using an automated BP monitor with participant seated comfortably for 5 minutes prior to the measurements. The average of three BP readings will be used as the measure for each visit. The same procedure will be followed at the 12-month study visit.

Justification: Uncontrolled BP is defined as average clinic systolic BP>140 mmHg or diastolic BP>90 mmHg following the guidelines set forth by WHO for CVD treatment and in accordance to the Nigerian healthcare policy. Adopting these guidelines currently instituted within the Nigerian healthcare system will ensure sustainability of the proposed study's procedures.

Secondary objective, endpoint, and justification

The secondary objectives are to:

- Compare in a cluster RCT of 30 HIV clinics, effect of the PF intervention versus self-directed condition (receipt of information for implementation of TASSH but no facilitation) on TASSH adoption and sustainability.
- Determine the mediators of adoption and sustainability of TASSH across the 30 HIV clinics at 12 months and 24 months respectively.

Secondary outcomes are:

- Rate of adoption and sustainability of TASSH across the PHCs at 12- and 24 months respectively.
- The mediators of TASSH across the HIV clinics at 12 and 24 months.

Justification: The proposed outcome of adoption and sustainability were HIV nurses because this study is a late stage T4 implementation research of which adoption and sustainability are standard endpoints. The rate of adoption of TASSH is defined as the proportion of patients who were diagnosed with HTN by the HIV nurses; received lifestyle counseling and antihypertensive treatment from HIV nurses. Sustainability of TASSH is defined as the maintenance of TASSH adoption at the PHCs at 24 months (one year after the end of the intervention). The following measures will be used to assess the mediators of TASSH via self-report and are based on the constructs of the CFIR framework including: 1) inner setting characteristics of the

clinics; 2) intervention characteristics, and 3) implementation process measures. Inner setting measures include implementation climate, implementation leadership, and the organizational culture domain of the organizational social context scale. Intervention characteristics measures include the Organizational Readiness to Change is assessed with the Evidence Scale-12 Items. Implementation process measures include: the external change agent support is a 3-item tool that evaluates support provided by external facilitators; and the Organizational Readiness to Change (Facilitation Scale-8-items), which evaluates organizational capacity to facilitate change will be used to evaluate implementation process measures focused on CFIR Engaging construct.

Hypotheses

Hypothesis 1: Systolic BP reduction will be greater in the HIV clinics randomized to the PF intervention than those in the self-directed condition at 12 months.

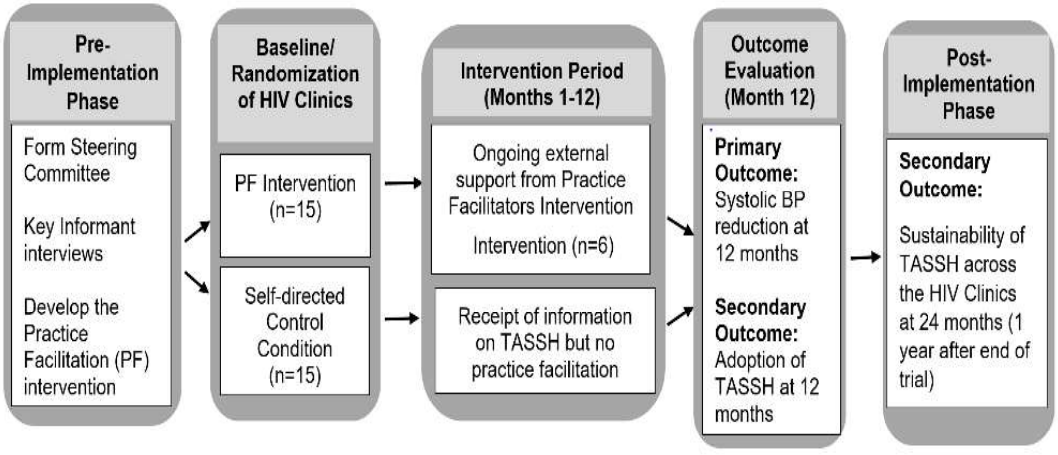
Hypothesis 2: The rates of adoption and sustainability of TASSH will be higher in the HIV clinics randomized to the PF intervention than those in the self-directed condition at 12 and 24 months respectively.

Hypothesis 3: Inner setting (implementation climate, leadership support), intervention characteristics, and implementation process will influence

Methods

Overall Design

Figure 1. Study Design



This study uses a mixed-methods hybrid type II effectiveness-implementation design. We plan to implement the study in three sequential phases: a **pre-implementation phase**, in which we will use CFIR to develop a context-specific PF strategy; and assess barriers and facilitators of integrating TASSH into the HIV clinics for management of HTN; an **implementation phase**, during which we will compare, in a cluster RCT of PHCs and among 960 HIV+ patients with uncontrolled HTN, the effect of PF versus a self-directed condition (i.e. receipt of information on TASSH without PF) on systolic BP reduction at 12 months (primary outcome); and a **post-implementation phase**, in which we will use RE-AIM to compare the effect of PF vs. self-directed condition on adoption and sustainability of TASSH at 12 and 24 months respectively (secondary outcomes). We will also assess the mediators of the adoption and sustainability of TASSH at 12 and 24 months. Components of the PF strategy will include: **(a)** Formation of an advisory board of key stakeholders at all levels of care

including the Lagos State AIDS Council Agency, who will provide leadership support for adaptation and integration of TASSH into HIV clinics. The board will provide leadership support for the adaptation and integration of TASSH into HIV clinics; **(b)** Use of a train-the-trainer model [from our previous trials],[19, 30] to train a cadre of experienced nurses from the Lagos State Directorate of Nursing to serve as practice outreach facilitators (POFs); and **(c)** Training of the HIV clinic nurses on the TASSH protocol for BP measurement, CV assessment, initiation of treatment with antihypertensive medications, and referral of complicated cases. As shown in **Figure 1**, all 30 HIV clinics enrolled during the pre-implementation phase, will be randomly assigned to either the PF intervention (N=15) or the self-directed condition (N=15). Once randomized, the clinics will participate in the 12-month implementation phase (intervention period) followed by a 12-month post-implementation period to assess its intervention sustainability. The primary outcome is *change in systolic BP* from baseline to 12 months. The secondary outcomes are *adoption* [proportion of patients who were correctly diagnosed with HTN, received lifestyle counseling and antihypertensive treatment]; and *sustainability* [maintenance of TASSH uptake at the HIV clinics at 24 months].

Methodology and outcomes for the implementation and the post-implementation phases will be guided by RE- AIM. The HIV clinics will be recruited from the network of 67 HIV clinics, who are part of the 100 primary care practices managed by the Lagos State Healthcare Board (LSPHB). We will leverage NIMR's connection with the LSACA and LSPHB to facilitate recruitment.

Scientific Rationale for Study Design

This study will utilize an implementation science framework for integrated HIV/NCD care programs by evaluating the effectiveness of a practical and replicable strategy to implement TASSH across HIV clinics in Lagos. Effective strategies for implementing evidence-based interventions are typically multi-level, and tailored to the practice context. However, PHCs in LMICs with weak healthcare systems, like Nigeria, lack the expertise needed to coordinate multilevel system changes without assistance. A practical implementation strategy to overcome this barrier is practice facilitation (PF) via provision of external expertise on practice redesign, and a tailored approach to provision of evidence-based care. Practice facilitation provides external expertise on practice redesign, and promotes a tailored approach to implementing systems changes to improve patient outcomes. Using a mixed methods design, we will develop a context-specific PF strategy to help HIV clinics implement TASSH, and then evaluate in a cluster RCT of 30 HIV clinics and 960 PLWH with uncontrolled HTN, the effect of PF strategy on systolic BP reduction as well as the adoption and sustainability of TASSH as an integrated routine practice in HIV clinics within Lagos State's primary care delivery network.

Study Population for the pre-implementation and implementation phases

Pre-implementation phase
This phase will involve 70 participants, who are steering committee members, key stakeholder or user testers (Nurses, physicians, patient advocate, Directors HIV clinics). Eligibility criteria for study participants are outlined below.

Inclusion criteria

- Be an adult aged 18 years and older.

- Ability to provide consent.

Exclusion criteria

- Inability to provide informed consent.
- Being deemed unable to comply with the study protocol

Implementation phase

The study implementation phase will be conducted at 30 HIV clinics located in Lagos, Nigeria. Sites and participants for the proposed study will be recruited from the list of over 67 HIV clinics registered with the Lagos State Healthcare Board. The NIMR will recruit 960 patients from 30 HIV clinics from this list under the guidance of Lagos State AIDS Control Agency, which funds comprehensive care for its HIV patient network in Lagos State. Note that this means recruitment of about 32 participants at each of the HIV clinics. Eligibility criteria for study participants are outlined below.

Inclusion criteria

- Be an adult aged 18 years and older.
- Attends one of the 30 HIV clinics.
- Have a diagnosis of HTN with uncontrolled blood pressure, i.e. BP is 140-179/90-100 mm Hg.
- Ability to provide consent.

Exclusion criteria

- BP>180/110 mm Hg;
- history of chronic kidney disease, heart disease, diabetes
- Stroke,
- pregnancy
- Inability to provide informed consent.
- Refusal to participate in the study.

Screen Failures

Screen failures will be referred to the PHCs for further management as is done in routine practice.

Strategies for Recruitment and Retention

The research staff will conduct the screening, consent, enrollment, and all study assessments. The study will recruit 30 HIV clinics from the network of 67 HIV clinics, who are part of the 100 primary care practices managed by the Lagos State Healthcare Board (LSPHB). All 67 HIV clinics are affiliated with the Lagos State AIDS Control Agency, which utilizes LSPHB to provide comprehensive primary care services to PLWH. Eligible HIV clinics will be selected from areas geographically distinct from one another. Once a clinic agrees to participate, their director will be asked to sign an MOU and identity 2 HIV nurses to be trained. Eligible patients will be identified from the HIV clinics during routine visits. Each clinic will recruit 32 patients using these inclusion criteria: 1) patient receiving care at the clinic; 2) adults 40 years and older; 3) BP 140-179/90-100 mm Hg; and 4) can provide informed consent. Exclusion criteria: 1) BP>180/110 mm Hg; history of chronic kidney disease, heart disease, diabetes or stroke, pregnancy; 2) inability to provide consent; and 3) refusal to participate.

SECTION 4: Study Intervention

Description of Study Intervention and its Administration

The practice facilitation intervention has three components, which are all described below along with the mode of delivery.

Formation of the advisory board to guide PF intervention: Advisory board members will be constituted from the Steering Committee members. It will comprise leaders from the Directorate of Nursing, physicians, HIV clinic nurses, leaders from the Lagos State Primary Healthcare Board (LSPHB), leaders from the Lagos State AIDS Control Agency, and patient advocates.

Development of the practice facilitation strategy. Components of the PF strategy are described below.

Training of the POFs using a train-the-trainer model: After randomization and recruitment of POFs, we will start the intervention with a "kick off" learning session, where we will review components of the TASSH protocol; quality improvement methods; the study timeline and evaluation plan with the POFs. Additionally, the POFs will be training to coach the HIV nurses on *Engaging*, *Enhancing*, and *Evaluating* their tasks as part of this intervention. POFs will carry out this function via onsite and remote supportive supervision of the HIV nurses. The basis of the strategy is to *Engage* the HIV nurses (via monthly phone calls to address barriers that the HIV nurses may have in performing their duties), *Enhance* the HIV nurses (via onsite visits quarterly to observe and supervise them in their duties) and *Evaluate* the HIV nurses (via onsite supervision and use of learning communities). Study staff will certify and re-certify the POFs as trainers yearly using a train-the-trainer model.

Identify site champion and coordinator: To ensure buy-in, each PHC is required to identify a site champion and coordinator (the POFs) who will serve as the implementation team. Site leadership is also required to sign a memorandum of agreement that describes all project activities in which staff are required to participate.

Build consensus for quality improvement targets: Onsite meetings with the POFs will occur bi-weekly for the first month and then monthly thereafter to facilitate practice changes to support the implementation of TASSH at the PHC. At the first onsite meeting, the HIV nurses will review baseline data on the proportion of their patients with HTN, review the TASSH protocol, and set targets for the PHCs.

Implement practice changes to support TASSH implementation: This activity will be conducted accordingly:

Assessment of participant screening practices.

Coaching of the POFs and provision of performance feedback and tracking to their progress and activities.

Peer-to-Peer Collaboration: The goal of the peer-to-peer collaborations is to provide a community in which POFs can share challenges, lessons learned, and best practices with each other as well as with PHC nurses and leadership.

Training of the HIV clinic nurses on implementation of the TASSH protocol: The HIV nurses will be trained on Identifying, Counseling and Referring (ICR) of adult HIV patients with HTN using the 5 As counseling strategy (Ask, Assess, Advise, Assist and Arrange). Study staff will create a training module for the HIV nurses. Components of the module, including how the 5 As will be mapped onto the ICR approach are outlined below. Table 1 provides a brief summation of module. Eligible patients at the PHCs randomized to the PF intervention will receive the TASSH protocol in the following steps:

Identify HIV patients with uncontrolled HTN: trained HIV nurses will take patients' medical history (whether or not they have a diagnosis of diabetes, heart attack, stroke, heart failure, smoking).

Ask: Create a list of standardized questions that the HIV nurse will ask the patient. Measure patient's BP, if high, then ask the patient if they have been told they have hypertension.

Assess: Based on the BP level, ask additional questions about their weight, height, and their dietary habits. Record the information in the logging report, and refer the patient to the community health center using the reporting/logging system.
Next, they will measure the patients' weight, height, waist circumference and BP with a valid automated device following standard procedures and then conduct lab tests with point-of-care testing on blood glucose, lipids and urine dip stick. The information from the medical history, physical examination and laboratory tests are then used by the nurses to assess patients' CV risk with a validated WHO risk chart. Patients who meet eligibility criteria (<20% CV risk) are scheduled for treatment.
Initiate lifestyle counseling and medication treatment every 1-3 months: The nurses will next counsel eligible patients on lifestyle behaviors for 20 to 30 minutes (increased intake of fruits and vegetables, moderate physical activity and reduce salt intake).

Advise: Counsel the patient on lifestyle behaviors like salt reduction, weight loss, taking BP medications and adoption of a healthy diet.
Refer patients with complicated HTN to physicians for further care: The nurses will refer patients with BP >180 /110 or CV risk >20% or those with history of stroke, diabetes, chronic kidney disease, or heart failure) to physicians for further care.
Assist: Begin referral process for the patient. All patients with elevated BP are referred to the health center.
Arrange: Give the patient the phone number of the health center, the name of the physician assistant to contact when they get to the health center, and call the physician assistant at the health center to make an appointment for the patient. Finalize the referral, as needed, and make sure patient receive needed care.

Table 1: TASSH Treatment Cascade and HIV Nurse Activities

Activities	Description
Take Patient History	The HIV Clinic Nurse will ask the following questions: Have you been told by a doctor you have heart failure? Have you been told by a doctor you have stroke? Have you been told by a doctor you have diabetes? If the answer to any of the above questions is yes, the TASSH nurse will refer the patient to a doctor.
Examine the Patient	The HIV Clinic Nurse will: Take Anthropometric Measures. Conduct a blood pressure check.
Cardiovascular Risk (CV) Assessment	The HIV Clinic Nurse will: ~~Assess blood glucose using Finger Stick Test.~~ ~~Assess protein in urine using Urine Dip Stick.~~ Assess CV risk using the World Health Organization CVD Risk Chart.
Lifestyle Counseling	The HIV Clinic nurses will advise patient about lifestyle behaviors (i.e. diet & physical activity).
Treat or Refer	The HIV Clinic nurses will prescribe hypertension medications to patients. If a case is complicated, the nurse will refer the patient to a doctor.

Duration and content of training modules
Each POF will be required to work with their assigned HIV clinics for 12 months. Over the 12-month period, each POF will conduct 13 site visits to the HIV clinics (2 in the first month, and then monthly thereafter) plus monthly peer-to-peer telephone support calls to the nurses.

Randomization, Measures to minimize bias, and Blinding
Randomization will occur at the level of PHC. All 30 HIV clinics enrolled will begin the study as part of the pre-implementation phase for 12 months, after which they will be randomly assigned to either the PF intervention (N=15) or the self-directed condition (N=15). Once randomized, the PHCs will participate in the 12- month implementation phase (intervention period) followed by a 12-month post- implementation period to assess its sustainability.

Randomization will occur in 5 cohorts of 6 PHCs every 6 months for 30 months and will be stratified by cohort to ensure balance over time. Upon completion of recruitment for each cohort, the clinics will be randomized in a 1:1 ratio to either the PF intervention or self-directed condition (i.e. receipt of information on TASSH implementation without PF). The sequence of randomization will be generated by Dr. Troxel, and kept in secure electronic format inaccessible to study sites, in accordance with CONSORT guidelines. Sites will be

informed of their randomization group by telephone. Because of the nature of the intervention, it is impossible to blind the patients, lay health advisors, and the study coordinators to the group assignment. The data analysts will remain blinded to treatment assignment until the completion of the implementation phase, defined as the period from baseline to 12-month follow-up(primary endpoint). During the post-implementation phase, the practice facilitators will leave the intervention sites and will have minor direct influence on the TASSH adoption. As the intervention concludes, data analysts will be unblinded following the primary endpoint. Preliminary database containing baseline and 12-month follow-up data will be locked upon unblinding for analysis.

Study intervention compliance (Group A).
Compliance with study interventions will be based on the following components of the intervention: a) training of the HIV nurses on BP measurements; counseling of eligible participants using the 5 A's; and referral of the participants to the primary health centers; b) training of the POFs on using the 3 E's to engage and enhance the activities of the HIV nurses. For this purpose, all training sessions will be audiotaped and videotaped for future use by the trainees. All trainees will complete a pre- and post-test on all study materials such that an adequate training will be based on satisfactory completion of the study materials after training. Finally, we will employ the *see one, do one and teach one* strategy to make sure that trainees acquire the necessary skills. Finally, with respect to training in referral of study participants to the primary health centers, the HIV nurses will be required to use electronic data capture which will be tracked for completion regularly.

Description of Usual Care (Group B).
HIV nurses based at Group B facilities will be trained on the 5As and referral of the participants to the health center. However, they will not receive practice facilitation from the POFs. Participants attending PHC randomized to Group B will receive standard care offered by that facility.

Study Intervention Discontinuation and Participant Discontinuation/ Withdrawal

Discontinuation of Study Intervention: Given that this study is a late stage T4 implementation trial, and given that the intervention proposed is a health systems practice facilitation strategy with minimal or no risk for the participants, we do not anticipate discontinuation of the study intervention.

Participant Discontinuation/Withdrawal: Because the study intervention is a health systems practice facilitation rather than a specific patient intervention, we do not anticipate that participants will discontinue the study intervention, but remain in the study for follow-up. That said, participants may withdraw voluntarily from the study or study investigators (PIs) may discontinue a participant from the study. Adverse events that will result in withdrawal of participants from the study include development of complications of hypertension and serious adverse events as determined by the DSMB. All cases of study discontinuation and participant discontinuation/withdrawal from the study will be documented separately in electronic formats. In addition, a dedicated Case Report Form (CRF) page will be used to capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

SECTION 5: Training, Monitoring, Quality Control and Assurance

Training of the HIV nurses and Practice Outreach Facilitators . See section 7 above. In addition, the study staff in Nigeria will receive ongoing training on the appropriate execution of the study protocol.
Study monitoring and quality control will be provided as follows.

Training of the study team, HIV nurses and POFs will be overseen by the principal investigators.
Oversight of study protocol will be monitored by an independent Data Safety Management Board (DSMB), which will be formed to monitor the safety of the study subjects, the validity and integrity of the study activities, as well as the data from the study. The general responsibilities of the DSMB are to:
Review the research protocol and plans for data and safety monitoring.
Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.
Monitor external factors to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study. For example, a systematic trend showing poorer, rather than increased, BP control or cardiovascular risk profile, in the intervention vs. the control condition.

Make recommendations to the NHLBI, IRB, and investigators concerning continuation or discontinuation of the trial(s).
Protect the confidentiality of the trial data and the results of monitoring by ensuring that computerized data files (quantitative and qualitative) are password protected. Any back-ups made of the computerized data will be put on separate hard drives which will also be password protected. Only named research staff will have access to the data onsite and offsite.

Implementation of the study protocol will be monitored by the study team in Nigeria, which comprises of the PI in Nigeria and the research staff (i.e. Research Coordinator, Research Assistant), who will be responsible for the monitoring and quality control of the study. The team meets bi-weekly to monitor the study progress, quality of data collection, adherence to the study manual/protocol, and good clinical practice. Study staff will be trained on all study procedures and documentation yearly. The study team will ensure that access to all forms and relevant documents is made available to members of the DSMB upon request, to facilitate their inputs or recommendations on how to improve study activities.

Study Procedure and Assessments

Study Procedures following randomization: After completion of the baseline data collection, all HIV clinics will be randomized in 5 cohorts of 6 clinics every 6 months for 30 months. Upon completion of recruitment of each cohort, the clinics are randomized in a 1:1 ratio to either the PF intervention group or the self-directed group. The randomization sequence will be generated by the study statistician and secured away from the clinics following CONSORT guidelines.

Study Visits: Eligible patients will be identified from the HIV clinics during routine visits. Once eligibility is confirmed, all patients regardless of their group assignment, will have a total of five study visits: baseline, 6, 12 months, 18 months, and 24 months post randomization. The structure of each study visit and the respective measures will be the same for each group (see study measures below). Beginning with the baseline visit, an average of 3 BP readings will be used as the measure for each study visit. The same procedure will be repeated at 6-, 12-, 18- and 24-month study visits.

Follow-up Study Visits (6, 12, 18, and 24 months): The research coordinator (RC) will meet with each patient to collect follow up data on primary outcome measure (BP measurements identical to that described for the baseline visit) and secondary outcomes. Study measures for both groups are similar and will be conducted in the same manner by the RC. Patients in the HIV clinics randomized to the Self-Directed Group will attend follow up study visits as scheduled while those in the clinics randomized to the PF Intervention will meet with their nurses every three months [for lifestyle counseling and treatment] in addition to the scheduled study visits.

On-time Follow-up Study Visits (6, 12, 18, and 24 months): On-time visit occurs within a +/- 3-months window of the expected follow-up date. For the 6-month follow-up visit, an on-time visit occurs between 3 and 9 months after baseline visit. For the 12-month visit, an on-time visit occurs between 9 and 15 months. For the 18-month visit, an on-time visit occurs between 15 and 21 months.

Baseline visits: The RC will confirm eligibility status and obtain informed consent from each patient. At baseline, we will measure the organizational and individual-level factors shown to affect implementation of evidence-based practices, including leadership, organizational capacity to change, individual attitudes toward evidence-based practices, and the degree of buy-in among practice facilitators.

SECTION 6: Study Measures

Primary Outcome: Change in systolic BP from baseline to 12 months. The SBP reduction in patients will be assessed as mean change in systolic BP from baseline to 12 months.

Secondary Outcomes are:

Adoption [proportion of patients who were correctly diagnosed with HTN, received lifestyle counseling and antihypertensive treatment]; and *sustainability* [maintenance of TASSH uptake at the HIV clinics at 24 months].

The mediators of TASSH across the HIV clinics at 12 and 24 months.

Assessment of Outcome Measures:

Blood pressure measurements: At baseline, three BP readings will be taken by trained research coordinator using an automated BP monitor with participant seated comfortably for 5 minutes prior to the measurements, following standard guideline. The average of three BP readings will be used as the measure for each visit. The same procedure will be followed at the 6, 12-month study visit. Uncontrolled BP is defined as average clinic systolic BP>140 mmHg or diastolic BP>90 mmHg following the guidelines set forth by WHO for CVD treatment28 and in accordance to the Nigerian healthcare policy.

Rate of adoption of TASSH is defined as the proportion of patients who were diagnosed with HTN by the HIV nurses; received lifestyle counseling and antihypertensive treatment from HIV nurses. For this purpose, adoption will be assessed by the following measures: 1) the number of hypertensive patients diagnosed by

the nurses using the WHO CVD risk assessment; 2) proportion of patients with HTN who received lifestyle counseling from the nurses; and 3) proportion of patients for whom the HIV nurses initiated treatment with antihypertensive medications. In order to assess this measure, the nurses will complete a questionnaire inquiring about the number of patients with uncontrolled HTN who received medication treatment and lifestyle counseling. For this purpose, all nurses will be required to keep an attendance log sheet for their patients' visits.

Sustainability of TASSH is defined as the maintenance of TASSH adoption at the HIV clinics at 24 months (one year after the end of the intervention). Sustainability will be assessed with a quantitative rate similar to adoption (as defined above) and qualitatively, based on interviews with nurses and clinic leadership at 24 months. The research coordinator will conduct the interviews with two nurses, and one key leadership personnel at each clinic. The interviews will be guided by CFIR and inquire about attitudes regarding the implementation of TASSH, barriers, facilitators, and implications for scalability. All interviews will be recorded, transcribed and analyzed with NVIVO Version 11.

The mediators of TASSH will be assessed via self-report. The mediators are based on the constructs of the CFIR framework including inner setting characteristics of the clinics, intervention characteristics, and implementation process measures as outlined below.

Inner setting measures include implementation climate, implementation leadership, and the organizational culture domain of the organizational social context scale.

Implementation Climate will be assessed with the Implementation Climate Scale that measures shared perceptions of the policies, practices, procedures, and behaviors that are expected, supported, and rewarded to facilitate effective EBP implementation. It has an overall Cronbach's alpha of .91 (18 items, 3 items on each subscale). The six subscales of EBP Implementation Climate are: focus on EBP (α=.91), educational support for EBP (α=.84), recognition for EBP (α=.88), rewards for EBP (α=.81), selection for EBP (α=.89), and selection for openness (α=.91).

Implementation Leadership will be assessed with the Implementation Leadership Scale (ILS) which has excellent reliability, convergent and discriminant validity. This is a brief 12-item measure with four subscales: Proactive Leadership (α=.95), Knowledgeable Leadership (α=.96), Supportive Leadership (α=.95), and perseverant leadership (α=.96) and a total score (α=.98).

Organizational Culture domain of the Organizational Social Context Scale is a 15-item Proficiency subscale that will be used to evaluate the practice capacity proficiency level of the HIV clinics. Proficient Organizational Cultures are those characterized by shared norms and expectations that the nurses are skilled service providers, and have current knowledge of the TASSH protocol. Items are completed using a 5-point rating scale ranging from 1 (never) to 5 (always) with measures such as responsiveness (e.g., *'members of my organizational unit are expected to be responsive to the needs of each patient'*) and competence (e.g., *'members of my organizational unit are expected to have up-to-date knowledge'*). Alpha reliability for the proficient culture scale is .89.

Intervention characteristics measures

Organizational Readiness to Change is assessed with the Evidence Scale-12 Items, which evaluates the strength of the evidence for the proposed change/innovation will be used to evaluate intervention process measures focused on CFIR's Evidence Strength & Quality and Relative Advantage construct. Each item measures the extent to which a respondent agrees or disagrees with the item statement on a 5-point Likert-type scale (1 = strongly disagree; 5 = strongly agree) and the Cronbach α=0.74.

Implementation process measures

External change agent support is a 3-item tool that evaluates support provided by external facilitators, the expectations about performance and improvement, and the ways to achieve the goal of the project**.** Items are scored on a 5-point Likert scale and the Cronbach α=0.77.

Organizational Readiness to Change105 (Facilitation Scale-8-items): which evaluates organizational capacity to facilitate change will be used to evaluate implementation process measures focused on CFIR Engaging construct. Each item measures the extent to which a respondent agrees or disagrees with the item statement on a 5-point Likert-type scale (1 = strongly disagree; 5 = strongly agree) and the Cronbach α=0.95.

Safety and Other Assessments:

Some personal and sensitive information may be requested from the patients during the course of this research study. Patients do not have to answer any questions they choose not to. They might feel inconvenienced by giving their time for the study visits and meetings with community health officers. Because patients' blood pressure recordings and survey responses will be used as a source of data for this study, there is a potential risk of a violation of their privacy. The study team will take steps to ensure that their private information is kept in a secured and locked safe.

Potential Benefits:

The intervention will benefit the participants by improving their blood pressure control, reducing their cardiovascular risk profile, and increasing their role as active participants in the management of their HTN. The ultimate aim is to develop a facilitation strategy that can be delivered nationally at little expense; thus, the benefit to others will occur when the intervention becomes a routine part of activities at the PHCs. Overall, the benefits of understanding effective methods for helping vulnerable populations, i.e. people living with HIV (PWH), reduce their cardiovascular risk far outweigh the remote possibility of a breach of confidentiality. The study may also have relevance to other PHCs by testing new strategies to enhance implementation of evidence-based interventions for improving hypertension control in high-risk populations.

Adverse Events and Serious Adverse Events: Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

Adverse Event: An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events if they increase in severity or frequency during the course of the study. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality meets any of the following criteria:

- results in study withdrawal;
- is associated with a serious adverse event;
- is associated with clinical signs or symptoms;
- leads to additional treatment or to further diagnostic tests; or
- is considered by the investigator to be of clinical significance.

Serious Adverse Event: A serious adverse event is any AE that meets the following criteria:

- fatal;
- life-threatening;

- requires or prolongs hospital stay (Hospitalisation for elective treatment of a pre-existing condition (known or diagnosed prior to informed consent signature) that did not worsen from baseline is NOT considered an SAE).
- results in persistent or significant disability or incapacity;
- a congenital anomaly or birth defect; or
- an important medical event

Assessment of Adverse Events: Participants will be evaluated for AEs at each study visit by the HIV nurse. Adverse events identified on the field will be reported to the study team immediately. A form will be completed by the study team to capture the relevant information. The study team will report the serious adverse events to the NIMR IRB. SAEs will also be reported to the LSPHB, to the Chair of the DSMB as well as to the sponsor. The DSMB has the authority to halt the implementation if it perceives that harm is occurring due to the intervention. Summaries of adverse events reports will be made to NIH in the yearly progress report or, at the end of year 5, in the final report, unless the nature of a particular event is such that it bears reporting to NIH immediately. Events will be followed for outcome information until resolution, stabilization, or until the subject completes the study. Subjects will be questioned regarding changes in their health and medications. Additionally, the subjects' overall health will be monitored as part of routine standard of care by community nurse; any changes to the subject's health will be noted in the subject's research record.

Time Period and Frequency for Adverse Event Assessment and Follow-Up: AEs will be recorded from the time the subject signs the informed consent through the subject's completion of the study. Events will be followed for outcome information until resolution, stabilization, or until the subject completes the study. All unresolved adverse events will be monitored by the investigator until the events are resolved, the post-study reporting period has ended, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. Any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study should be recorded in the subject's study chart and reported to applicable regulatory agencies according to current guidelines.

Reporting of Serious Adverse Event to NHLBI: Summaries of adverse events reports will be made to the NHLBI CTS representative on a bi-annual basis, unless the nature of a particular event is such that it bears reporting to the NIH immediately. These reports will be generated by the program staff and the PIs. This information will then be reported to the DSMB regularly or during its bi-annual meetings. All adverse events reporting shared with the DSMB at the bi-annual meetings will also be sent to the CTS. Consequently, unless the nature of a particular event warrants immediate reporting to the NIH, the CTS will receive adverse events reports twice a year.

Unanticipated Problems: Any incident, experience, or outcome that meets the following criteria:
Unexpected in nature, severity, or frequency.
Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in

the research); and suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Reporting of Unanticipated Problem to the IRB and NHLBI: Incidents or events that meet the Office for Human Research Protections criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. The following information will be provided when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB and NHLBI, if it is available:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.
- To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:
- Unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Data collection, handling, record keeping

A real-time electronic data collection system will be established in accordance with stringent data management protocols of Nigerian Institute of Medical Research (NIMR). Data will be entered into a web-based electronic database capture system called Research Electronic Data Capture (REDCap). Electronic data collection forms will be developed using the REDcap platform and deployed on tablets for the data collection. Data collection will be done by HIV nurses and hosted on a server at NMIR. These forms have in-built data validation and consistency checks. Dedicated study data managers at NIMR will review study data on a weekly basis, generate queries on outliers and send written queries to the field for correction and updates.

Access to source documents, case reports forms, other data and information

The Principal Investigators will be responsible for sharing and granting access to data generated from the study. Data will be shared among the investigators via an electronically secured method that encrypts data during transfer. The data will be reviewed by the PIs and, study data managers and study statistician on a monthly basis and issues raised will be communicated to the project coordinators to be addressed during the coordinator's periodic visits to the data collection sites in Nigeria. For essential documents, a paper form regulatory binder will be utilized. Paper records would be stored in a study-specific regulatory binder or file. The site Principal Investigator would approve all source documents before it is made accessible.

Statistical Considerations

Data analysis: primary outcome, associations to be studied, techniques to be used

This trial employs an effectiveness-implementation hybrid design examining the adoption of the TASSH intervention with a culturally tailored PF intervention for uptake in usual care for HIV treatment. Aim 1 will employ qualitative methods to explore inner setting variables, intervention characteristics, and implementation processes likely to influence successful uptake and sustainability of TASSH at participating PHCs. The goal of Aim 2 will be to determine the effect of the PF intervention on systolic BP reduction at 12 months (primary outcome) - the measure of clinical effectiveness of the PF intervention. It will be assessed as the mean change in systolic BP from baseline to 12 months. BP will be taken with valid automated BP device similar to our other trial.

Aim 3 will evaluate the difference between the intervention arms in adoption and sustainability of the TASSH program at 12 and 24 months. For analyses on this aim, a multilevel mixed model using an unstructured covariance matrix will be applied, with the outcomes defined as the proportion of participants within clinic who were diagnosed with HTN, received lifestyle counseling and treatment for HTN at 12 months (adoption) and the proportion of participants within clinic who have received screening, counseling and HTN treatment at 24 months (sustainability). Aim 4 will examine the mediators of adoption and sustainability of the PF intervention at 12 and 24 months.

Additional details regarding each of these analyses are discussed below.

Analysis for Aim 1: Qualitative Data Analysis for the Pre-Implementation Phase

The semi-structured interviews and user-testing interviews will be transcribed and entered into NVivo, version 11, for data analysis. We will use the framework approach to qualitative data analysis, a five- step process that involves: 1) familiarization (a process during which the researcher becomes immersed in the details of multiple sources of data to gain a general understanding of the content and to document initial impressions), 2) developing a theoretical framework (a process by which the researcher identifies emergent themes in the multiple sources of data using existing theories as a guide; these themes will be continually refined and compared to each other), 3) indexing (during which the researcher becomes further immersed in the data in order to refine identified themes and sub-themes), 4) summarizing data in an analytical framework (during which the researcher reduces materials into understandable but brief summaries of what was said by stakeholders), and 5) data synthesis and interpretation (which allows for comparison of themes and sub-themes against original transcripts, field notes, and audio recordings to ensure appropriate context). Following the framework approach, as described above, two to three research team members to reduce the potential for bias will independently code the data. Inter-rater reliability will be determined based on a subset of the data, for example, the interviews, and will be repeated until satisfactory agreement among raters is achieved (i.e., 80% of coded data). Discrepancies in coded data will be resolved by consensus. After systematically reading all transcripts, they will be coded into concepts reflecting the aim of this phase. For example, responses will be coded according to intervention characteristics likely to influence TASSH uptake within participating HIV clinics. Established procedures to enhance the robustness of our analysis will be used, including analyses of codes that do not fit our coding scheme, development of an audit trail documenting analytical decisions, and member-checking presentations to the Steering Committee. The identified concepts will then be grouped into categories and themes uniting the categories will be

determined. A detailed analysis of the interviews should generate a conceptual model that elucidates barriers and facilitators of the uptake of TASSH within participating HIV clinics in Nigeria. It should also suggest modified facilitation strategies tailored to the clinics' context to overcome these challenges.

Analysis for Aim 2

Analysis for Aim 2 will consist of a repeated measures mixed-effects model for systolic BP (SBP), with fixed effects for time and intervention arm, and random effects for clinic. An interaction term be included for the intervention arm and time; this interaction, if non-zero, will indicate that the degree of change of SBP over time differs for those in the practice facilitation intervention compared to those in the self-directed condition. Also, for this aim assessments will include whether adjustment for any baseline characteristics is necessary, including such adjustments based on the change-in-estimate criteria.

Analysis for Aim 3

For adoption, the analysis will have one within person factor – Time (baseline and 12-month coded naturally as months [0 and 12]) – and one primary between-patient factor – (Randomization Group dummy coded as 0 = Self-directed Condition and 1 = Practice Facilitation). Fixed effects will be specified for time, randomization group and their interaction effect (group by time). The outcome measure will be a composite index for adoption of TASSH (defined as patients diagnosed with HTN, received lifestyle counseling and treatment for HTN by the HIV nurses). Additionally, the nurses will be nested within clinics creating a 3-level analytic model (observations nested within nurses nested within clinics). Random effects will be specified for clinics and for nurses, adjusting for the clustering of measures within nurse and nurses within clinic. Multilevel modeling software (SAS, Version 9, PROC MIXED) will be used to compute full information maximum likelihood (FIML) estimates of the model parameters. The PROC MIXED procedure will use an error structure that allows for the possibility of group differences in (a) the error variances at 12 months; and (b) the serial correlations of the baseline with the 12-month outcomes. For sustainability, the analysis will be repeated as described above but will be evaluated at 24 months instead of 12 months. Adoption at 12 months will be assessed using questionnaires completed by nurses and sustainability at 24 months will be assessed with site interviews and site visits. Levels of adoption and sustainability will be compared between the group that randomized to the PF intervention and the group randomized to the self-directed condition. The qualitative components of sustainability at 24 months will be assessed using interviews with nurses and clinic leadership. These interviews will be recorded, transcribed and entered into NVIVO Version 11 for analysis. The analytic plan will be similar to the qualitative methods described for Aim 1.

Analysis for Aim 4

This aim will assess the extent to which inner setting variables (e.g., implementation leadership, implementation climate, and organizational culture) affect the degree of adoption of TASSH as defined in Aim 3, and its sustainability at 24 months. Particular attention will be paid to the pathways via which this occurs. We will estimate a just-identified path model using the robust weighted least squares estimator to investigate relationships among the theoretical mediators of implementation climate, implementation leadership, organizational culture, organizational readiness to change, and external change agent support. Based on our conceptual model, we will test the direct effects from the theoretical constructs to the adoption components (individually). In addition to the direct effects, the indirect effects from each variable to adoption via inner setting variables will be estimated as the product of component direct effects and tested using bootstrapped 95% confidence intervals. Finally, we will estimate the direct effects of the

predicted model of adoption on SBP reduction. Predicted probabilities of the adoption and sustainability outcomes and SBP will be calculated from path model coefficients to elucidate the magnitudes of direct and indirect effects.

Methods for handling missing data:

Although we will attempt to retain as high a fraction of participants as possible, we acknowledge that some attrition is likely, leading to missing outcome values. The generalized linear mixed models proposed for the primary and secondary analyses incorporate an assumption of data that are missing at random (MAR), meaning that the likelihood of a value being missing depends on observable characteristics (e.g., sex or age). In sensitivity analyses, we will assess the impact of different assumptions about the missing data mechanism, and will determine the robustness of trial results to these different assumptions. We will consider the use of multiple imputations of missing data as an alternative sensitivity analysis.

SECTION 7: Ethical Consideration

Institutional Review Board Approvals for this study will be obtained from the NYU School of Medicine (NYU) and the Nigerian Institute of Medical Research (NIMR).

Informed consent

All study sites will be provided with a model informed consent form (ICF). It is expected that all sites will use identical informed consent forms. If needed, individual sites may adapt the ICF to meet institutional guidelines and policies. Procedural and risk content may not be removed from the model consent form. Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms used for this study are IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent or provide a thumb print for participants that are illiterate. This procedure will be followed prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. Consent may be written or given verbally. If written, a copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. *See Section 20.0 for inform consent forms*.

SECTION 8: Significance of Research

Potential value of the study: The intervention will benefit the participants by improving their blood pressure control, reducing their cardiovascular risk profile, and increasing their role as active participants in the management of their HTN. The ultimate aim is to develop a facilitation strategy that can be delivered nationally at little expense; thus, the benefit to others will occur when the intervention becomes a routine part of activities at the PHCs. Overall, the benefits of understanding effective methods for helping vulnerable populations, i.e. people living with HIV (PWH), reduce their cardiovascular risk far outweigh the remote possibility of a breach of confidentiality. The study may also have relevance to

other PHCs by testing new strategies to enhance implementation of evidence-based interventions for improving hypertension control in high-risk populations

SECTION 9 :Timeline

TIMELINE AND MILESTONES	YEAR 1				YEAR 2				YEAR 3				YEAR 4				YEAR 5			
	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Start up																				
Convene collaborative kickoff with project partners and subsequent weekly subcommittee meetings																				
Define roles and responsibilities of SC and establish meeting schedule																				
Establish DSMB																				
Announce project kickoff broadly/launch site recruitment and retention plan																				
Hire/train research and program staff																				
IRB application submitted/approved																				
Develop project website																				
Establish study databases, finalize baseline assessment survey and fidelity tracking tools (survey/non-clinical measures)																				
Complete practice facilitator training																				
Pre-implementation Phase																				
Conduct key informant interviews																				
Refine and finalize facilitation/intervention materials and protocols with participation of the Steering Committee																				
Implementation Phase (Intervention Period)																				
Baseline assessments of primary and secondary outcomes																				
Randomization of HIV clinics																				
Site retention activities																				
Post-Implementation Phase																				
Conduct interviews and site visits																				
Extract utilization and referral data from health record																				
Evaluation																				
Complete process evaluation assessments of implementation																				
Complete annual and end of program reports																				
Dissemination Activities																				
Development of dissemination toolkit components																				
Distribute briefing reports for stakeholders																				
Post materials and protocols on program website and distribute to dissemination partners																				
Develop and submit manuscripts																				
Distribute study findings through multiple communication channels																				
Attend national meetings to present findings																				

SECTION 10: Protection of Human Subjects

There is a pre-implementation phase, which includes tailoring the practice facilitation strategy through a formative evaluation with key stakeholder at the participating network of HIV clinics in Lagos, Nigeria. This will be followed by an implementation phase during which we will evaluate, in a cluster randomized controlled trial, the effect of the tailored practice facilitation strategy vs. a self-directed control condition among a sample of 960 people living with HIV (PLWH) with uncontrolled hypertension (HTN). Finally, in a post-implementation phase, we will evaluate the adoption and sustainability of the intervention across the 30 HIV clinics after the completion of the practice facilitation.

Proposed involvement of human subjects will comprise of intervention participants and trained nurses at the participating HIV clinics. As detailed below, they will be asked to complete surveys pertaining to their perceptions of intervention fidelity as well as participate in semi-structured interviews. We will also obtain participant-level data from assessment of participants' blood pressure. We will follow recommendations made for the responsible conduct and protection of human subjects in qualitative research and clinical trials.

Recruitment Strategy

Identifying HIV clinics: The NIMR will be responsible for all recruitment activities. NIMR has deep connections with the Lagos State Healthcare Board and its network of over 67 HIV clinics in Lagos, Nigeria given its previous work with these organizations. Currently, there are over 67 clinics affiliated with NIMR; we will recruit 30 HIV clinics for this study. Two Research Coordinators (RC) will be hired by NIMR to conduct the screening, consent, enrollment, and all study assessments. Dr. Ezechi will supervise recruitment and retention activities of the research staff.

Recruitment of HIV Clinics: We will recruit HIV clinics that are affiliated with the Lagos State Primary Health Care Board, which is also affiliated with the Lagos State AIDS Control Agency (LSACA). Dr. Ezechi will meet with clinic leaders to provide study overview. All eligible HIV clinics must be a NIMR-affiliated clinic - there are 67 across Lagos. Eligible clinics will be selected from areas geographically distinct from one another with equal urban/rural mix. Once a clinic agrees to participate, their key leadership personnel will be asked to sign a MOU and identity 2 nurses to be trained to deliver TASSH.

Participant recruitment strategy: The RCs will work with nurses to develop a recruitment strategy specific to the clinic. Once the nurse has identified a participant who meets the inclusion criteria, the person is given a telephone number of the RC to call if they are interested in the study. During the call, the RC will give a brief explanation of the procedures, including the following: that participants will have a 50-50 chance of being in the Practice Facilitation Strategy or Self-Directed Condition (depending on which group their clinic is randomized to); that not every participant is accepted into the study (this will be decided during the screening visit). If the person desires to participate at this point, an in-person appointment for the consent/screening visit is then set for the participant with the RC and nurse.

Characteristics of the study population during the pre-implementation and Implementation phase

Pre-implementation phase

This phase will involve 70 participants, who are steering committee members, key stokeholder or user testers (Nurses, physicians, patient advocate, Directors HIV clinics). Eligibility criteria for study participants are outlined below.

Inclusion criteria

- Be an adult aged 18 years and older.
- Ability to provide consent.

Exclusion criteria

- Inability to provide informed consent.
- Being deemed unable to comply with the study protocol

Implementation phase

The study implementation phase will be conducted at 30 HIV clinics located in Lagos, Nigeria. Sites and participants for the proposed study will be recruited from the list of over 67 HIV clinics registered with the Lagos State Healthcare Board. The NIMR will recruit 960 patients from 30 HIV clinics from this list under the guidance of Lagos State AIDS Control Agency which funds comprehensive care for its HIV patient network in Lagos State. Note that this means recruitment of 32 participants at each of the HIV clinics. Eligibility criteria for study participants are outlined below.

Inclusion criteria

- Be an adult aged 18 years and older.
- Attends one of the 30 HIV clinics.
- Have a diagnosis of HTN with uncontrolled blood pressure, i.e. BP is 140-179/90-100 mm Hg.
- Ability to provide consent.

Exclusion criteria

- BP>180/110 mm Hg;
- history of chronic kidney disease, heart disease, diabetes
- or stroke, pregnancy
- Inability to provide informed consent.

Refusal to participate in the study.

Inclusion of vulnerable populations

Participants with cognitive impairment are not eligible to participate.

Sources of materials

These will include paper-and-pencil as well as web-based questionnaires, audiotaped sessions and semi-structured interviews and standard participant chart data. All data will be used specifically for research purposes. The data analyst, under the supervision of the study statistician (Dr. Troxel) will work with the Dr. Ezechi from NIMR the Research Coordinating Center to send de-identified participant level files to NYU. NYU will give the data managers in NIMR a range of unique study identifiers to assign to participants. The analyst will keep a table of these identifiers once they have been assigned for the duration of the study. Using this method, we will ensure that confidentiality of participants is maintained but that participants who are observed more than once will have the same study ID in each extract. A pre-defined set of measures will be exported from the data warehouses into a de-identified Excel spreadsheet or delimited text file.

Potential risks and protection against risks

Though we expect the level of risk due to this intervention to be minimal, potential risks to the participant may include the following:

Violation of participant privacy and confidentiality

Loss of confidentiality is the greatest potential risk to study subjects. We will obtain written consent from all study participants who participate in surveys and interviews; however, no identifying information will be included on the transcripts of interviews or surveys. As part of the process involved in obtaining written informed consent, all participants will be reminded that their responses are confidential and that they may refuse to participate in the project or withdraw at any time without explanation, and further, that such an action will in no way affect their treatment or future interactions with their providers. Also, if a participant is

uncomfortable during a research encounter, they may stop at any time. All survey data entered into the research database will be protected by confidential entry codes. Names will be replaced with identification numbers. All health record data will be de-identified prior to transfer from the data warehouses to the central repository managed by NYU. Locked file cabinets will be used to store materials with identifying information (e.g., participant consent forms). Only members of the research team will have access to participant's personal information file. Study data will be transmitted to Dr. Troxel and the data analyst for data processing using only secure methods (e.g., encrypted email). All electronic audiotaped data will be saved on a secure server housed by NYULH and backed up daily or weekly depending upon the receipt of data. Participant health information will be confined to a secure server that is not connected to the Internet. All computers are password protected and on a private LAN network. No file and database servers are accessible to the public through the Internet. Prior to inclusion in any data set (internal and external), data will be stripped of all identifying information. Finally, the web-based surveys will be accessed via a HIPAA compliant application. The data collected for this study will be used strictly for the purposes stated in this grant application and will only be available to relevant research staff at the Nigerian Institute of Medical Research, Washington University in St. Louis and NYU. IRB approval will be sought prior to any data collection involving human subjects. Finally, all identifiable participant health information will be obtained and managed in accordance with the HIPAA Privacy Rule, 45 CFR Parts 160 and 164.

Anxiety

There is a potential risk that participants may feel uncomfortable or anxious during the audiotaped sessions and/or semi-structured interviews. To mitigate this potential challenge, the study staff member who conducts the semi-structured interview will be trained to act professionally and address all participants' concerns. Participants will also be reminded that the tapes are only for research purposes and will not influence their relationship with the provider. Moreover, participants will be reassured that the tapes will be saved in a secure and confidential database that only the study staff will have access to, and that have the right to ask that the tapes be deleted if they feel sensitive information was discussed during the session that they do not want the research team to hear.

Adequacy of protection against risks

Recruitment and informed consent

Study staff will be responsible for recruitment of subjects and data collection. Researchers are required to be trained in Human Subjects and HIPAA policies and procedures and the handling of data to ensure the confidentiality in order to obtain Institutional Review Board (IRB) approval from NYULH. Clinic key personnel and staff will be told about the study at a group meeting. Participation is voluntary and written consent is obtained from participants prior to conducting baseline procedures, and after a detailed explanation of the study is provided by the research staff. Survey data will be entered into a password protected laptop computer or tablet using a web-based portal housed on a secure NYULH server. Once potentially eligible participants are referred to the study staff, the study coordinator will provide a more in-depth description of the study to the participant in clear, easy-to-understand language. If the participant remains interested in participating, the study coordinator will provide a copy of the consent form for the participant to read; if the participant asks for help or indicates that they have a problem reading the consent form, the study coordinator will read the consent form to the participant. If the participant agrees to participate, s/he will sign the consent form or provide a thumbprint in lieu of a signature for participants who cannot read or write.

Potential Benefit of Proposed Research to Human Subjects and Others

The intervention is expected to benefit the participants by improving their blood pressure control, reducing their cardiovascular risk profile, and increasing their role as active participants in the management of their HTN. The intervention is expected to benefit the participants. The ultimate aim is to develop a facilitation strategy that can be delivered nationally at little expense; thus, the benefit to others will occur when the intervention becomes a routine part of activities at the HIV clinics. Overall, the benefits of understanding effective methods for helping vulnerable populations, i.e. people living with HIV (PLWH), reduce their cardiovascular risk far outweigh the remote possibility of a breach of confidentiality. The study may also have relevance to other HIV clinics by

testing new strategies to enhance implementation of evidence-based interventions for improving hypertension control in high-risk populations.

SECTION 11 : Data and Safety Monitoring Plan

In compliance with NIH requirements, we will establish a data and safety monitoring plan (DSMP). The purpose of the DSMP is to ensure the safety of participants and the validity and integrity of the data. Personnel involved in the monitoring activities will include:

- The Principal Investigators on this application.
- Designated medical monitor (a physician in our program who will provide consultation on medical risks
- and who will review adverse events).
- Internal Committee (The PIs, and the Co-Investigators on the present proposal).
- Institutional Review Board.

The data and safety-monitoring plan will comprise the following elements:

- Reporting of adverse events to the IRB and to NIH trials: Adverse events will be reported to the IRBs. Summaries of adverse events reports will be made to NIH in the yearly progress report or at the end of year 5, in the final report, unless the nature of a particular event is such that it bears reporting to NIH immediately.
- A detailed plan to deal with serious events that may arise, such as blood pressures that indicate a hypertensive emergency that occur during the baseline and follow-up periods (these are the only times that any of our personnel will take such measurements). The plan will include a step-by-step algorithm to deal with such events.
- The PIs and the co-Investigators will meet yearly to review adverse events reports, patient complaints if any, and dropout rates. Data will be provided at those meetings by the investigators on key variables that may indicate harm, including changes in blood pressure and self-reported adherence to medication regimen for people living with HIV (PLWH). The biostatistician will evaluate confidentiality and integrity of the database, and the procedures for recording and storing confidential files. The investigators will also review the elements of the plan to deal with emergencies.
- Protect the confidentiality of the trial data and the results of monitoring.

SECTION 12: Study Records Retention

This study will comply with the NYULH policy on research record retention. Specifically, all research data accessed by NYUSM study personnel will be maintained on MCIT DataCore-approved EDC systems, and accessed only via MCIT-approved computers via authorized and approved study personnel.

SECTION 13: Publication and Data Sharing Policy

Our commitment to translating efficacious interventions into routine “real world settings” and to supporting the potential for sustainability has informed the selection of partners, the design of the practice facilitation intervention, and the governance structure for the project, as well as our strategies for disseminating insights from the implementation (process) and outcomes evaluation. This plan will be executed by a Dissemination Committee that we will set up for the purpose of this study. Through regular meetings with the Steering Committee throughout the grant period, we will engage key stakeholders at the participating HIV clinics, Lagos State AIDS Control Agency (LSACA), and the Lagos State Primary Health Care Board to assist with refining our approach to enhance relevance and usability, disseminating findings at regular intervals and providing expertise on the external context in which the study approach is being implemented. Upon the successful completion of the project, the study PIs in collaboration with key agencies such as the Nigerian Ministry of Health will work together to develop effective measures for rolling out the intervention to control sites

throughout Lagos State. This roll-out effort will include periodic refresher trainings for HIV clinic nurses at the control sites and collaborations with regional/ state primary healthcare agencies to establish effective protocols for integrating TASSH within their respective clinics.

The dissemination of evidence-based health interventions in low income countries has been hampered by a lack of "infrastructure for marketing and distribution." Key to all forms and stages of dissemination will be NYU Langone Health's (NYULH) robust communications and marketing department, which is designed to disseminate best practices in public health and care processes as well as the development of external publications and press releases as program findings emerge. In addition, the National Institute of Medical Research (NIMR's) communication office will handle the dissemination to key stakeholders. To facilitate dissemination more broadly, we will develop a dissemination toolkit that provides guidance on how to support implementation of practice facilitation in the HIV clinics. Our dissemination toolkit will have four main components: 1) presentations at scientific conferences; 2) publications in high impact relevant peer-reviewed journals; 3) establishment and maintenance of a website for dissemination of research findings; and 4) presentation of study findings at stakeholders' forums.

In accordance with NIH requirements, we will register the trial in clinicaltrials.gov, as mandated under Public Law 110-85, no later than 21 days after the first subject is enrolled. We will also report the summary of all results no later than one year after the completion date. The Clinical Research Support Unit and Human Research Regulatory Affairs offices support investigators at NYULH in initiating, conducting, and managing studies by providing guidance in several crucial areas, including post-award management and compliance with grant policy requirements (e.g., registration and maintenance of ClinicalTrials.gov accounts). We will ensure that our informed consent documents clearly state that information related to the trial will be posted on ClinicalTrials.gov. All participants will need to initial this statement to signify that they understand and agree to this requirement. The team will also disseminate research findings through presentations at international meetings. We will publish findings in peer-reviewed journals, and other venues.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. The principal investigator will be responsible for developing publication procedures and resolving any potential authorship issues related to this study.

Section 14: List of Investigators

Role	Name	Contact Information
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Section 15: Funding

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Section 16: Budget

s/n	COST CATEGORY	Amount (USSD)
1	Salaries and Wages (including consultants)	12,000
2	Travels	7,680
3	Other Direct Cost	149,440
4	Total Direct Cost	169,120
5	Indirect Cost	13,530
	GRAND TOTAL	182,650

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Section 18: Attachments/Enclosures

Indicate the documents that have been attached to this protocol:

	CHECKLIST	YES/NO

1.	CV of investigators	X
2.	Informed Consent	X
3.	Patient Information Leaflet (*If applicable*)	X
4.	All questionnaires	X
5.	Letters from collaborators, supervisors, certificates/letter (s) of approval etc	
6.	Signed investigators responsibilities declaration	
7.	Others please, specify	