Strengthening Referral Networks for Management of Hypertension Across the Health System (STRENGTHS): A Cluster Randomized Controlled Trial

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Sponsor:

The National Heart Lung and Blood Institute (NHLBI)
Grant Number: U01HL138636

Version: 9.0 – 2020-09-10
Version Date: 2020-09-10

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List of Abbreviations

AE	Adverse event
AMPATH	Academic Model Providing Access to Healthcare
BP	Blood Pressure
CDM	Chronic disease management
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DCC	Data coordinating centre
DSMB	Data Safety and Monitoring Board
EMR	Electronic medical record
ES	Executive secretary
FGD	Focus group discussions
HIT	Health Information Technology
ICC	Intra-class correlation
KII	Key informant interviews
LMICs	Low and middle-income countries
Lower-MICs	Lower middle-income countries
MDD	Minimum detectable differences
mHealth	Mobile Health
MTRH	Moi Teaching and Referral Hospital
NCD	Non-communicable disease
NHLBI	National Heart Lung and Blood Institute
PN	Peer navigator
RA	Research assistant
SAE	Serious adverse event
SD	Standard deviation
SBP	Systolic blood pressure
SOP	Standard operating procedure
UC	Usual care

1. Synopsis

Title	Strengthening Referral Networks for Management of Hypertension Across the Health System (STRENGTHS)
Lead Institutions	Moi University College of Health Sciences (MUCHS) and Moi Teaching and Referral Hospital (MTRH)
Investigators	Dr. Constantine Akwanalo (MUCHS & MTRH) Dr. Jemima Kamano (MUCHS & MTRH) Dr. Benson Ng'ang'a (MTRH) Prof. Violet Naanyu (MUCHS) Dr. Ann Mwangi (MUCHS) Dr. Timothy Mercer (University of Texas, Austin) Dr. Rajesh Vedanthan (New York University) Dr. Sonak Pastakia (Purdue University) Dr. Jonathan Dick (Indiana University) Dr. Makeda Williams (NHLBI)
Study Sites	Primary, Secondary & Tertiary Health Facilities in Uasin Gishu County, Trans Nzoia County, Busia County, Bungoma County and Nandi County
Planned Study Period	2017 - 2022
Objective	This study aims to evaluate whether an integrated intervention composed of peer support and a health information technology tool can improve referral adherence and improve blood pressure among patients with complicated hypertension in a lower middle-income country setting
Study Design	This is a cluster randomized controlled trial that will compare: **Intervention:** An integrated intervention composed of peer support and a health information technology tool to support referral services **Control**: Usual referral service A total of 8 clusters representing unique referral networks will be randomized equally at the level of the secondary health facility.
Number of Participants	1600 patients with hypertension who are referred either to a higher or lower health facility
Inclusion Criteria	Age ≥ 18 years and either: 1. Patients with complicated hypertension (meet criteria for referral up the network), defined as any of: a. Uncontrolled (SBP ≥ 140 or DBP ≥ 90) on 3 or more anti-hypertensive medications b. Have signs or symptoms of end-organ damage (dyspnea on exertion, leg edema, reduced urine output, focal weakness) c. Have suspected secondary causes of hypertension (age <35 years, HIV, or pregnancy) d. Any other concerning condition that the clinician suspects to be attributable to hypertension for which they would seek a higher level of care

	Or: 2. Patients with stable, uncomplicated hypertension (meet criteria for referral down the network), defined as controlled BP (SBP < 140 and DBP < 90) for 3 or more consecutive visits **and** no evidence of new end-organ damage
Exclusion Criteria	1. Acute illness requiring immediate medical attention 2. Terminal illness 3. History of coronary artery disease or stroke 4. Inability to provide informed consent
Primary Endpoint	One-year absolute mean change in SBP
Secondary Endpoints	One-year change in overall CVD risk as measured by the QRISK2 score **Process Metrics** Up-referral completion rate Down-referral completion rate Median referral completion time Referral appropriateness

2. Study Flow

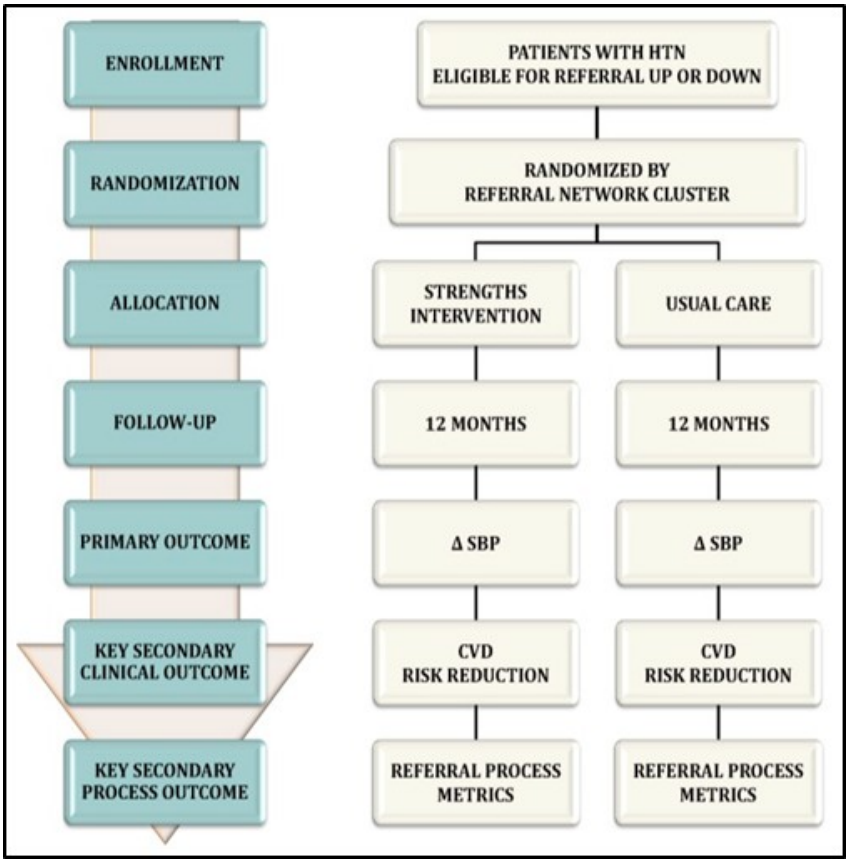

Figure 1: STRENGTHS Study Flow

3. Background and Rationale

Hypertension: Burden and Implementation Gaps. Elevated blood pressure (BP) is the leading preventable cause of early death and disability globally,[1,2] and 75% of patients with hypertension live in LMICs.[3] In Kenya, prevalence of hypertension is nearly 25%.[4] similar to. Despite many evidence-based interventions to manage hypertension, gaps in implementation persist, especially in LMICs.[3,5,6] In lower-MICs, only 37% of known hypertensives were on treatment, with less than 10% of them being adequately controlled.[5]

Referral Networks. The Kenya Health Referral Strategy 2014-2018 highlights an effective referral system as crucial to improving equitable access to essential health services.[7] However, referral networks in Kenya[8] and similar lower-MICs are characterized by referral non-adherence and delays in referral completion.[9-11] Public sector health systems in lower-MICs often employ a multi-level system spanning a primary- to specialty-care continuum,[12] with a tripartite system of primary, secondary, and tertiary care.[13] Patients with complicated hypertension require referral up the network for specialty care, as well as advanced diagnostic and treatment modalities.[13] Patients with stable, uncomplicated hypertension can be referred down the network where care is geographically decentralized and task-shifted to lower levels of providers, reducing costs and increasing access to care.[7] Effective referral networks have improved outcomes in maternal and child health,[13,14] HIV,[15,16] and CVD.[17] Furthermore, in resource-limited settings, strong referral networks are essential to improve the efficiency of resource utilization and guarantee equitable provision of healthcare services.[18] Therefore, strong referral networks provide an evidenced-based foundation upon which interventions for hypertension can be implemented and evaluated in lower-MICs.

Multi-Level Factors Impacting Referral Networks for Hypertension. Rates of referral adherence in lower-MICs is low. Successful referral completion was only 37% among patients found to have hypertension or at elevated CVD risk following community-based screening in Bangladesh, Guatemala, Mexico and South Africa.[17] In Burkina Faso, referral adherence was 20% among patients referred for hypertension.[9] The causes of referral non-adherence are multifactorial.[7,17,19] Patient-related factors include lack of time, cost, transport distances, and limited understanding of the rationale.[17,20-22] Provider-level factors include poor documentation and limited human resources for health.[17] Health system-related factors include lack of integrated health records,[23,24] long patient waiting times, and the complexity of navigating larger health facilities.[17]

Peer Support. Peer-based care approaches leverage unique patient-patient interactions built on shared disease experiences to influence behavior change.[25] Peers have successfully been used to improve adherence to HIV medicines [26-29] and have effectively supported chronic disease management.[7,30-33] Peer navigators have been used to improve linkage to and retention in care for patients with HIV,[34,35] as well as improve healthcare utilization in mental health[36] and cancer.[37,38] To date, peer navigators have not been evaluated in the context of strengthening referral networks to improve hypertension control.

HIT. HIT, including integrated EMRs and mHealth, are a key strategy in LMICs for NCD management,[39-41] and can improve documentation and data capture, which are significant barriers to effective referral networks.[13,23,42] Our systematic review of mHealth for NCDs in sub-Saharan Africa highlights the use of HIT for patient follow-up and peer networks among patients with NCDs.[43] However, the evidence base is limited, with an urgent need for more rigorous implementation research of HIT interventions.[43] Specifically, it is not well known if HIT, in combination with peer support, can strengthen referral networks for hypertension control.

4. Specific Objectives

The objective of this research is to utilize the PRECEDE-PROCEED framework to conduct transdisciplinary, translational implementation research focused on strengthening referral networks for hypertension control. The central hypothesis is that HIT integrated with peer support will be effective and cost-effective in strengthening referral networks, improving BP control, and reducing CVD risk among patients with hypertension in western Kenya. We hypothesize that HIT and peer support will synergistically address barriers to hypertension control at the patient, provider and health system levels. We further hypothesize that changes in referral network characteristics may mediate the impact of the intervention on the primary outcome, and that baseline referral network characteristics may moderate the impact of the intervention. To test these hypotheses and achieve the

overall objective, we will conduct a two-arm cluster randomized trial comparing: 1) usual care vs. 2) referral networks strengthened with an integrated HIT and peer support intervention. We will pursue the following specific objectives:

1. Evaluate the effectiveness of HIT and peer support on one-year change in SBP and CVD risk reduction.
2. Conduct mediation analysis to evaluate the influence of changes in referral network characteristics on intervention outcomes, and a moderation analysis to evaluate the influence of baseline referral network characteristics on the effectiveness of the intervention.
3. Conduct a process evaluation using the Saunders framework, evaluating key implementation measures related to fidelity, dose delivered, dose received, recruitment, reach, and context.
4. Evaluate the incremental cost-effectiveness of the intervention, in terms of costs per unit decrease in SBP, per percent change in CVD risk score, and per DALY saved.

5. Concise Statement of Design

We will evaluate the effectiveness of HIT and peer support for strengthening referral networks for hypertension control by conducting a non-blinded two-arm cluster randomized trial comparing: 1) usual care vs. 2) referral networks strengthened with an integrated HIT and peer support intervention (Figure 2). The primary outcome measure will be one-year change in systolic blood pressure (SBP) and a key secondary outcome will be change in CVD risk score.

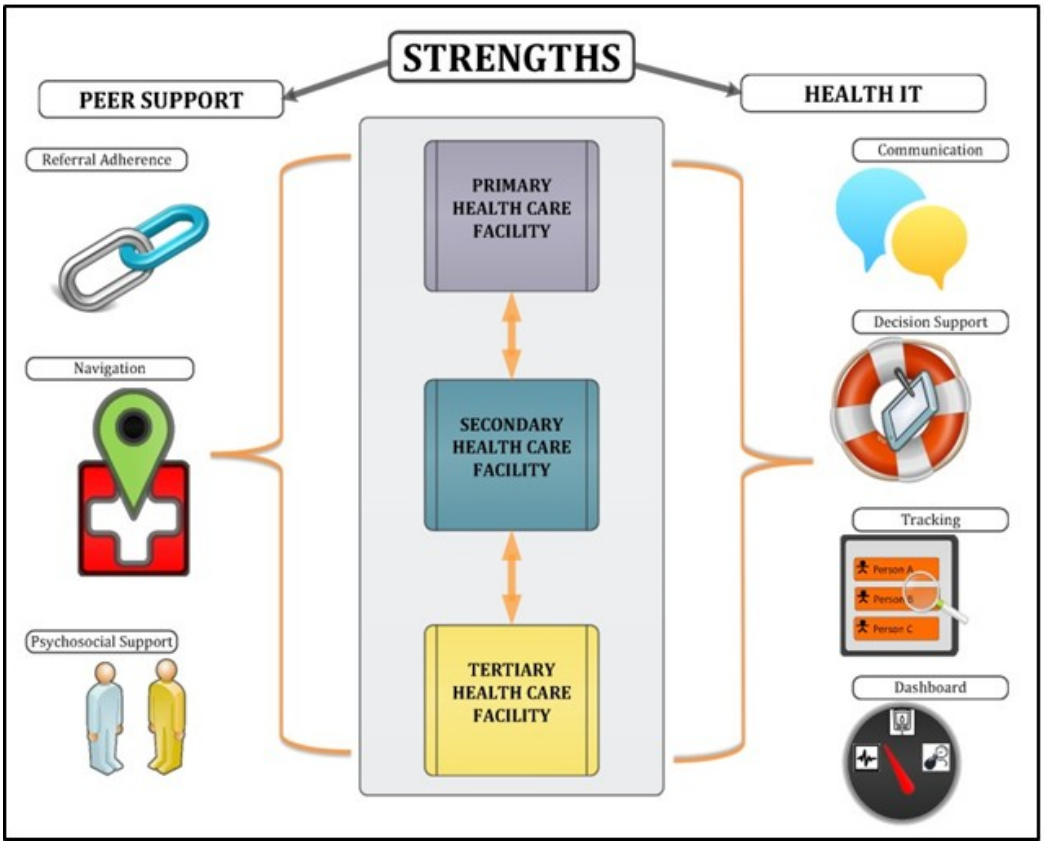

Figure 2: The Integrated HIT and Peer-support intervention

6. Participant Recruitment and Follow Up

Inclusion Criteria

Adult patients (≥18 years) who are enrolled in AMPATH's CDM program with hypertension, who meet criteria for referral up or down the network, will be eligible for inclusion in the trial.

For referral up, criteria are:

- Patients with complicated hypertension, defined as any of:
    a. Uncontrolled (SBP ≥ 140 or DBP ≥ 90) on 3 or more anti-hypertensive medications
    b. Have signs or symptoms of end-organ damage (dyspnea on exertion, leg edema, reduced urine output, focal weakness)
    c. Have suspected secondary causes of hypertension (age <35 years, HIV, or pregnancy)
- Any other concerning condition that the clinician suspects to be attributable to hypertension for which they would seek a higher level of care

For referral down, criteria is patients with stable, uncomplicated hypertension, defined as controlled BP (SBP < 140 and DBP < 90) for 3 or more consecutive visits **and** no evidence of new end-organ damage

Exclusion Criteria

- Acute illness requiring immediate medical attention
- Terminal illness
- History of coronary artery disease or stroke
- Inability to provide informed consent

Recruitment Approach

The clinicians will be sensitized about the study and the eligibility criteria. They will then invite AMPATH CDM patients with hypertension and eligible for referral from the health facility to enroll in the study on the day of their routine clinic visit. On that day, research team members will briefly describe the research study to the potential participant. They will then perform a short interview using the screening for eligibility tool which documents the age of patient, type of referral and reason for referral (Appendix 1). Patients meeting eligibility criteria will then be asked their willingness to participate in the study, and if willing will proceed to the informed consenting stage. Patients not meeting eligibility or unwilling to participate further will be referred back to their clinician to continue with clinical care as per the clinician's management plan. For referral networks randomized to the HIT and peer support intervention arm, participants will be informed of the HIT functionality and the availability of peer navigators who can assist them with the referral process. Extreme care will be taken to fully explain the benefits and risks of the research study, before written consent is obtained. The consent will be written in lay terminology at approximately 6th grade (USA) level (Appendix 2). Individuals will be free to refuse to participate in the study at any time during the period of the study. A refusal will not impact the health care available to the individual in any manner. Access to care will not be impacted in any manner by an individual's decision to opt out of this research project.

Randomization

The unit of randomization will be a cluster, which consists of a geographically separate, distinct hypertension referral network within the overall AMPATH CDM program. There will be a total of eight clusters (referral networks), each of which will be centered around a secondary-level health facility: Mosoriot, Kwanza, Kiminini, Webuye, Kocholya, Bunyala, Butula, and Nambale (Figure 3). Each of these secondary-level facilities constitute the last step in their respective referral network before reaching the common, tertiary level of MTRH, Busia County Referral Hospital, Kitale County Referral Hospital, or Bungoma County Referral Hospital. In addition, each secondary-level facility has a number of primary-level health facilities that feed into it. Four of

the clusters will be randomly assigned to the intervention arm, and four will be randomly assigned to the control arm. Randomization will be stratified by the size of the secondary-level health facility.

Clusters*	Primary Level	Secondary Level	Tertiary Level
Mosoriot	Mogoget Birbiriet Itigo Lelmokwo Kokwet Ngechek	Mosoriot Sub-county hospital	Moi Teaching and Referral Hospital
Kiminini	Bikele Sister Fredah	Matunda Sub-county hospital	Kitale County Referral Hospital
Kwanza	Kaisagat Namanjala	Kwanza Sub-county hospital	
Webuye	Milo	Webuye County hospital	Bungoma County Referral Hospital
Kocholya	Angurai Changara Malaba Kamolo Akichelesit Aboloi Moding	Kocholya Sub-county hospital	
Bunyala	Budalangi Bulwani Busagwa Mukhobola Osieko Rukala Sirimba Sisenye	Port Victoria Sub-county hospital	Busia County Referral Hospital
Butula	Bumala A Bumala B Ikonzo Sikarira	Khunyangu Sub-county hospital	
Nambale	Lwanyange Madende Musokoto	Nambale Sub-county hospital	

Figure 3: Referral Network Facilities in the STRENGTHS study

*Unit of randomization

Blinding

Trial participants, research assistants and the research coordinator will not be blinded. This is because the nature of the intervention, peer support, cannot be concealed from participants, or the research staff who will be doing enrollment and follow-up at the clinic sites and as such will be aware if there is a peer or not in the facility. The data analyst/biostatistician and co-investigators will be blinded, unaware which participant is assigned to which arm of the trial. The PI's (CA and JK) see patients at the cardiology and medical outpatient clinic at MTRH, and might interact with study participants during their clinical duties. They might therefore become aware, during the course of their clinical duties, of the trial arm to which a study participant has been

assigned. Should this happen, the PIs are expected to implement usual clinical care regardless of the patient's participation in the trial. No further action will require to be taken.

Usual Care
Within the AMPATH CDM program, usual management at the primary and secondary levels involves an attempt to control BP with up to 3 anti-hypertensive medications before referral, under the supervision of a mentoring clinician who visits the lower level facility on a rotating basis. Frequency of clinical visits will depend on clinical circumstances and level of care, mimicking real-word conditions. The process for referrals will continue as it is currently practiced within the AMPATH CDM program and Kenyan MOH. For patients with complicated hypertension requiring referral up the network, the referring clinician writes a referral letter on a standardized, blank referral form, with demographic information of the patient and reason for referral. This referral letter is then given to the patient, who is responsible for presenting it to the receiving facility and arranging the referral visit. For patients with stable, uncomplicated hypertension requiring referral down the network, a counter-referral letter, and/or copies of clinical records, are given to the patient to take back to their primary facility, although this process is not consistently adhered to. There is no dedicated psychosocial or health system navigation support in the usual care arm.

Intervention
Those randomized to the intervention group will receive clinical care for hypertension in the same manner as those randomized to the usual care group. Reasons for referral will also be the same in the two groups. The change in referral process is the intervention which is an integrated HIT tool and peer support.

HIT: AMPATH uses AMRS, a customized version of OpenMRS.[44] AMRS is centrally hosted and accessed by tablet via the Internet with all data simultaneously available to all users of the system, independent of their location. This facilitates both real-time data collection and monitoring. Our HIT intervention will augment AMRS to support a referral system in four ways: 1) communication: facilitate data sharing by all providers and peer navigators across all levels of the health system; 2) decision support: provide clinical decision support to facilitate appropriate patient referrals; 3) tracking: generation and sharing of real-time patient referral lists; and 4) dashboards: create a platform for monitoring key evaluation metrics. The system will prompt for referral if indicated but also allow the user to self-initiate a referral. Providers and peer-navigators will access the designed referral dashboard for a clinic to review patient referrals, identify patients who made their referral appointment, and track patients who have been referred back to the referring site. Key referral process metrics (described below under "Secondary Outcomes") will be available in real-time for providers and peer navigators to monitor and act upon.

Peer Support: The peer support component of the intervention will involve "peer navigators" at each level of the referral network – primary, secondary and tertiary, titled "Community Peer Navigators", "Facility Peer Navigators", and "Central Peer Navigators", respectively. The Community Peer Navigators will cover a catchment area within the community surrounding each primary level health facility. The Facility Peer Navigators will be stationed at the secondary level health facilities in each referral network. The Central Peer Navigator will be stationed at the tertiary level, MTRH. The roles of the peer navigators will be drawn from those described in the HIV and oncology literature,[45-50] but adapted and contextualized. The peer support intervention has three main functions: 1) referral adherence: link clinicians and patients to provide referral logistics support; 2) navigation: help patients navigate the complex health system;[51] and 3) psychosocial support: leverage their shared disease experience to help patients overcome barriers to health seeking behavior. Referral adherence support entails ensuring patients know the "what, where, when, and how" of the referral process. The peer navigators will be equipped with an HIT tool, as described above, so they can see the same data as the clinicians in order to track and follow referred patients appropriately. When a clinician at the primary level refers a patient to a higher level of care, the Community Peer Navigator covering that patient's community catchment area will automatically be alerted on their HIT tool so they can contact and meet the patient, and review referral logistics. The Community Peer Navigator will then complete a referral navigation form on the HIT tool, which will automatically trigger a notification to the clinician and Facility or Central Peer Navigator at the receiving facility, alerting them of the incoming referral. The second major role of the peer navigator is health system navigation, especially at the tertiary level. Here, the peer navigator can

personally and physically receive a referred patient and walk them through the complexities of registration, scheduling, triage, and diagnostic work-up in order to streamline the referral process and ensure patients are not lost in the complexity of the system.[52] Furthermore, peer navigators will meet with patients after the clinic visit to provide any follow-up navigation between the pharmacy, laboratory, or imaging. Communication between the Central, Facility, and Community Peer Navigators will be automated via the HIT tool to ensure seamless communication and data-sharing. The third major role of the peer navigator is to provide psychosocial support to patients and their families, helping them overcome individual-level barriers to health seeking behaviors, drawing from the innate trust inherent in their shared disease experience.[25] Peer navigators at all levels will be trained to provide education, motivational interviewing, and psychosocial support.

Participant Follow Up

Participants will have three visits for both study arms: a baseline visit upon enrollment, a six-month visit, and a 12-month visit. In both arms of the trial, if the patient does not present to the clinic for the 6 month or 12-month visit, the patient will be traced by the research team. Missing data resulting from loss to follow up will be handled as detailed in section 10.

Study Withdrawal

Individuals will be free to refuse to participate in the study and withdraw at any time during the period of the study. Withdrawal will not impact the health care available to the individual in any manner. Access to care will not be impacted in any manner by an individual's decision to opt out of this research.

7. Study Outcomes

Clinical Efficacy Outcomes

Primary outcome

One year absolute change in mean BP
The systolic blood pressure at baseline will be compared to systolic blood pressure after 1 year of follow up.

Secondary outcomes

One-year change in overall CVD risk as measured by the QRISK2 score
QRISK2 score is a computerized algorithm for predicting the ten-year risk of developing CVD events. The factors that enter into the calculation of the QRISK2 score include: Age 25-84 years, sex, ethnicity, smoking status, diabetes status, family history of coronary artery disease in first degree relatives below the age of 65 years, chronic kidney disease stages 4 and 5, atrial fibrillation, rheumatoid arthritis, cholesterol / high density lipoprotein ratio, systolic blood pressure, body mass index.

A score of 10% or more suggest a 10% risk of primary CVD events in ten years and warrants intervention to reduce the risk. It's not used among patients who already have a heart attack or a stroke.

One-year mortality rate
Death by the end of the 1 year follow-up

Hospital admissions
Number of self-reported hospital admissions for any cause among participants over one year follow up

CVD complications
Any self-reported cardiovascular complications including hypertensive crises, heart failure, Stroke and Acute myocardial infarction

Change in CVD risk factors and behaviors
Baseline risk factor profile compared to profile at 1 year of the various CVD risk factors as assessed using a standardized CVD risk factors and behaviors screening questionnaire

Medication adherence
Changes in self-reported adherence to hypertension medication at one year from baseline as assessed using the Voils adherence questionnaire[53]

Process Outcomes

Referral Process Metrics
- Up-referral completion rate
- Down-referral completion rate
- Median referral completion time

Process Evaluation

- Fidelity (quality of intervention delivery as assessed using a checklist-based field observation of peer navigators, written tests for peer navigators at baseline and six months, and separate focus group discussions for peer navigators, participants and clinicians, see Appendix 3 for full Process evaluation protocol)
- Dose delivered (completeness)
- Dose received (exposure and satisfaction)
- Recruitment
- Reach (participation rate)
- Context

Cost Effectiveness Outcomes
- Incremental cost effectiveness ratio

8. Adverse Events and Serious Adverse Events

An AE is defined as any untoward or unfavourable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

An SAE is a defined as any AE that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

The safety observation period extends from the time the signed informed consent is obtained through the completion of the final study visit. All patients enrolled in the trial who experience an SAE will be managed at their nearest health facility according to the Kenya MOH cardiovascular disease guidelines,[54] with referral to higher levels of care if needed.

Reporting Procedures

Given that peer navigators and research assistants are the study staff who will have direct contact with study participants, we anticipate that an AE or SAE will first be detected by the peer navigator or the research assistant. Should the PN be the first to detect a probable AE or SAE, they will be expected to report to the RA within 1 hour of detection. Once an RA is aware of an AE or SAE, they will fill out the electronic AE/SAE reporting form (Appendix 4), and inform the research coordinator via phone, both RA actions will be expected to be complete within 1 hour. The filed form will then be reviewed by one of the three clinical Kenyan investigators within four hours, who will then ascertain the AE/SAE. If ascertained as a true AE/SAE, the investigator will be expected to generate a report to NHLBI, IREC and the DSMB within 24 hours. All peer navigators and RAs will be trained on AEs and SAEs detection and reporting. All SAEs and AEs will be captured on electronic CRF. The three Kenyan clinical investigators (a monthly rota will be created and maintained by the research coordinator) are responsible for continuing to follow all AE and SAE reports (whether or not related to study intervention) until resolution or until the event is considered chronic and/or stable by the investigator and/or other physician who has the responsibility for the patient's medical care. All SAEs will require expedited reporting by the PI to the study's DSMB, IREC/IRB, and NHLBI. An expedited report of an SAE will be submitted by email and must be reported to the DSMB, IREC/IRB and the NHLBI within 24 hours of the event being reported to the Investigator. The expedited report will be followed by a detailed, written AE/SAE report using the standard study AE/SAE reporting form (Appendix 4) as soon as possible. Follow up information will be availed if asked for by DSMB directly, or from NHLBI or its representatives. A master log of all AE's/SAE's will be maintained and the PI will submit a statistical report from the log to the DSMB at least two weeks prior to all scheduled DSMB meetings.

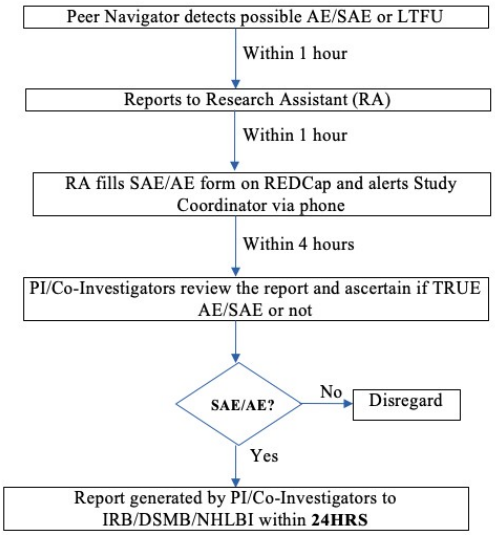

Figure 4: Adverse Events and Serious Adverse Events Reporting Procedure

9. Data Collection, Handling and Record Keeping

Data collection, handling and record keeping

For the primary and secondary clinical efficacy outcome, the baseline and 12-month assessments will be measured by trained study staff to ensure standardization and uniformity of measurement. Data will be collected on covariates we hypothesize may be related to our outcomes. These include patient demographics, socioeconomic and education status, clinical comorbidities, CVD risk factors, health behaviors, geographic location, referral level, and provider level of training.

For the process outcomes, data will be collected at whatever level of care the patient clinically requires, in order to mimic real-world practice and accurately map the patient wherever he or she falls within the referral network. Semi-quantitative and qualitative data for the process evaluation, including observation, surveys, interviews, and focus group discussions. Observational data will not contain any patient identifiers. These data include transcripts of mabaraza[55] (traditional form of community assembly), focus group discussions, and interviews; completed clinician surveys; and observation notes (study activities preceding the trial portion). Mabaraza, focus group discussions, and interviews will be digitally audio-recorded and uploaded with a coded identification number (no identifying names) as an audio file to an electronically secure database. Similarly, the clinician surveys will be de-identified and coded, and the data extracted and stored in the same electronically secure database. These research data will be stored in an electronically secure database protected by password that will be known only to key research team members and the Study Coordinator. Once uploaded to the electronically secure database, the data will be deleted from the digital recording device and the original surveys containing identifying information will be destroyed. Electronically captured data will transfer to the research database at the time of entry into the handheld device through a secure connection tunnel. All data on mobile devices will be encrypted and stored on the device's internal memory. All paper data collection forms will be reviewed by the Study Coordinator and Data Manager for completeness. Once validated, any sheets containing directly identifiable information and consent documentation will be separated and added to the site's secure storage locker. The remaining, de-identified pages will then be placed in a separate storage locker prior to data entry. Only key investigators and study personnel will have access to individually identifiable private information about human subjects. Transcription of the audio files will occur in Kenya and will be done by the trained research assistants. These transcripts will also be stored in an electronically secure database on a password-protected computer.

For the cost-effectiveness outcomes, cost data will be obtained during the implementation of the intervention and health service utilization data will be obtained from the AMRS. These data will be collected during the course of the project implementation by research staff. Two sets of costing instruments will be used, one completed by study participants, and the other completed by research staff. The instruments completed by participants capture healthcare utilization and expenditures, work loss, and transportation costs and can be used to quantify cost offsets from intervention participation. The instruments completed by research staff capture all relevant labor, materials, supplies, and contracted services costs for all activities required to deliver the intervention. All data collected on paper forms will be transferred to the research database using double data entry.

Electronically captured data on REDCAP will transfer to the research database at the time of entry into the handheld device through a secure connection tunnel. All data on mobile devices will be encrypted and stored on the device's internal memory. All paper data collection forms will be reviewed by the Study Coordinator and Data Manager for completeness and the presence of pre-specified "danger" values. Once validated, any sheets containing directly identifiable information and consent documentation will be separated and added to

the site's secure storage locker. The remaining, de-identified pages will then be placed in a separate storage locker prior to data entry. Only key investigators and study personnel will have access to individually identifiable private information about human subjects.

Protections against risk to data

The following principles and procedures for data collection will be followed at the research site in order to minimize risk and protect confidentiality:

- Data will be collected on coded forms, which do not include other personal identifiers
- Only the tracking form will have the participant's name and identifiable information
- Study records will be stored in locked cabinets in a locked room
- Only the study personnel will have access to the data and the codes
- All computerized information will be protected by access codes known only to key investigators and certain designated staff members
- No data will be published with participant names
- Data that are contained on a digital audio recording device will be PGP-encrypted
- All staff members will be trained to keep participants' information confidential, and will be informed of the penalty for breach of confidentiality

The consent form signed by the participant will provide written assurance that all individual data collected in the study will be kept confidential to the extent provided by the Privacy Act of 1974. AMPATH will provide file security so that confidential data are not released. Specifically, participants will be informed that: (1) the only people who will know that they are research participants are members of the research team and, if appropriate, their physicians or health care providers; (2) no individual identifying information about them will be disclosed to others, except if required by law; and (3) when the results of the study are published or discussed in conferences, no information will be included that would reveal their identity.

Any material that is digitally audio-recorded will be uploaded with a coded identification number (no identifying names) as an audio file to an electronically secure database. These research data will be stored in an electronically secure database protected by password that will be known only to the Principal Investigator and the Study Coordinator. Once uploaded to the electronically secure database, the data will be deleted from the digital recording device. Transcription of the audio files will occur in Kenya. These files will also be stored in an electronically secure database on a password-protected computer.

All clinical patient-level data will be entered into the AMRS as per AMPATH's standard operating procedures. A separate, password-protected research database will retrieve data from AMRS via access that will be controlled through user authentication. All data collected on paper forms will be transferred to the research database using double data entry. Electronically captured data will transfer to the research database at the time of entry into the handheld device through a secure connection tunnel. All data on mobile devices will be encrypted and stored on the device's internal memory.

All data management will be carried out by CITI-certified research staff members, and all data will be stored on dedicated, password-protected computers. Any data stored on portable media will be PGP-encrypted, in order to ensure security of the data. Paper forms will be stored for the duration of the study, and for one year following in order to allow verification of any data as needed for reporting and publication purposes. The paper forms will then be shredded. The electronic data with a coded identification number only (and no identifying names) may be kept indefinitely, in a secure manner as described above.

To prevent inadvertent disclosures and ensure subject confidentiality, data entry and document storage for materials containing directly identifiable information (i.e., coversheets) will be handled by key investigators or the Study Coordinator. The Study Coordinator will be responsible for the secure handling and storage of survey documents for the duration of research activity at the study site. Once activities have been completed, coversheets will be collected and forwarded to the AMPATH research office, where they will be stored in a secure, locked cabinet within a secure, locked room. To minimize the number of people with access to the

coversheet data, all data entry will be conducted under the direct supervision of the Study Coordinator. Once identifiable data has been entered as described, paper-based documents will be returned to secure storage.

10. Data Analysis

We will quantify the effectiveness of an integrated HIT and peer support intervention for strengthening referral networks to improve BP control and reduce CVD risk. The primary outcome measure is one-year absolute mean change in SBP. A key secondary outcome measure is one-year change in overall CVD risk as measured by the QRISK2 score, which has been validated for calculating 10-year CVD event risk for Black Africans.[146-154]

For the cost-effectiveness analysis, only net incremental costs, after factoring in cost offsets that may result from improved health, will be included as the numerator in the CE analysis as these are the relevant costs for decision makers. As part of the costing analysis, we will also identify which activities drive the overall costs, and how costs would change if specific activities are added or eliminated.

Minimum detectable difference (MDD)

The study is powered to detect improvement in SBP in the intervention arm compared to usual care. We expect that each of the eight referral networks will enroll at least 200 participants. Based on other studies in the region we expect a difference of 4 to 10-mmHg[56] between the two groups at month 12. The power calculations summarize MDD in the primary outcome for the comparison between the two groups. Using a two sided test with a Type I error rate at 5% (alpha = 0.05), and a standard deviation of 15mmHg (SD values for change in SBP found in the literature ranges from 10 to 20).[57,58] Table 1 presents power for the comparison across different combinations of ICC ranging from 0.02 to 0.08, consistent with prior studies using SBP as the outcome[58-60] for a range of MDD of 4 to 10 mmHg. We assume that up to 15% of enrolled participants will be lost to follow up.

Table 1: Estimated power over a range of ICC and MDD values

MDD	ICC			
	0.02	**0.04**	**0.06**	**0.08**
4	52	32	24	20
6	85	61	46	37
8	98	84	70	58
10	99	96	87	77

Methods of Analysis

Our analyses for both the primary and secondary outcome will be conducted according to the principle of intention to treat, in which every cluster is analyzed according to the assigned intervention, regardless of the treatment actually received. We will use a repeated measures mixed-effects model for SBP, with fixed effects for time and intervention arm, and random effects for cluster and individual. The model specification is:

$$E\left(Y_{itk}\right)=\alpha+\beta_1 I\left(t=6\right)+\beta_2 I\left(t=12\right)+\beta_3 I\left(t=6, intervention\right)+\beta_4 I\left(t=12, intervention\right)$$

where Y_{itk} is SBP for the i^{th} individual at the t^{th} time in the kth cluster and I() represents the indicator of the event in (). The hypothesis test for the coefficient β_4 will be a test of whether SBP after 1 year differs for those in the intervention compared to those in the usual care condition.

We will compare key independent variables across the trial arms to ensure balance of the randomization process, and assess whether adjustments for any baseline characteristics is necessary and make adjustments in the model to estimate treatment effects as needed. The analysis will be stratified by predefined strata of referral up and referral down. For modeling QRISK2, we will use the transformation log (-log(QRISK2)) because the risk score ranges from 0% to 100%. The model will be fit using maximum likelihood with the software package R.

Approach to handle missing data

Individuals who are missing outcome data at 12 months will be traced by the research team to ascertain and alleviate dropout bias in our trial.[61-63] The follow-up sample will enable us to form an imputation model for the missing outcomes. Using the subset of individuals who dropped out but whose SBP was ascertained after tracing, we will fit a regression using 12-month outcome as the dependent variable, and baseline covariates and the most recently observed outcome at month 6 as the independent variables, and use the model to generate predicted (imputed) values of outcomes for those not traced. We will account for uncertainty using multiple imputation.[64] In addition, the generalized linear mixed models proposed for the primary and secondary analyses incorporate an assumption of data that are missing at random, meaning that the likelihood of a value being missing depends on observable characteristics. We will employ sensitivity analyses via pattern mixture modeling[65-67] to examine potential for systematic bias attributable to missing values that cannot be ascertained by tracing participants (expected to be up to 15% of the sample, as above).

11. Protection of human subjects

Informed Consent

The proposed study will be conducted following strict guidelines for the protection of the rights of participants. Informed consent will be signed by all participants following screening. Extreme care will be taken to fully explain the benefits and risks of the research study, before consent is obtained. Written informed consent will be obtained from all participants. The consent form (Appendix 2) will be written in lay terminology at approximately 6th grade level. Participation in the study will be discontinued if the participant chooses to stop participating in the study and notifies the study team. Participants will be allowed to withdraw from the study, should they choose to, without risk of any discrimination, or any risk of impact on their clinical care and they can choose to seek clinical care at any facility (AMPATH, other public sector or private sector) that they wish.

The residents of study site areas may come from economically disadvantaged backgrounds. We will continue the policy of AMPATH of not providing excessive monetary compensation for study subjects beyond reimbursement to cover travel expenses and time. This policy will be followed in order to ensure that consent is freely given without risk of “monetary coercion.” Vulnerable populations such as children, neonates, human fetuses, and any individuals <18 years old will not be included in the study. Pregnant women who are hypertensive will be eligible for participation in the trial but their clinical management will remain per the usual clinical care. Within each referral network cluster, the relevant MOH facilities will be contacted and receive information on the different study procedures anticipated through completion of this project.

Data Safety and Monitoring Board

An independent DSMB has been established for this study to ensure the safety of trial participants. This DSMB is composed of independent faculty members from the Moi University College of Health Sciences, Aga Khan University Hospital (Kenya), and the MOH, who are not otherwise involved with the project. Membership of the DSMB includes the following expertise: Clinical Cardiology, Clinical Trials, Community-Based Research, Implementation Science, and Ethics. All members are independent and free of any project-related financial interest.

After constitution, the DSMB formulated a charter to guide DSMB operations, a living document that can be reviewed at regular intervals to determine whether any changes in procedure are needed, but cover the areas described below.

Responsibilities of the DSMB
The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and monitoring the overall conduct of the study. The DSMB is an independent group and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB can be asked to make recommendations, as appropriate, to the NHLBI and/or the appropriate institutional review board (IRB) about:

- Efficacy of the study intervention (DSMB only)
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety
- Notification of and referral for abnormal findings

The DSMB will also be expected to coordinate with the TREIN/Hy-TREC consortium coordinating centre for preparing regular DSMB reports.

Organization and Interactions
Communication between the study staff and DSMB members is primarily through the DSMB administrator (ES). It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at open DSMB meetings. The DSMB ES will provide an unbiased staff interface for the DSMB, especially during executive sessions. The ES is responsible for assuring the accuracy and timely transmission of the final recommendations and DSMB minutes.

Scheduling, Timing, and Organization of Meetings
The DSMB convened prior to initiation of the trial portion of the study to review the study protocol and give approval of the study trial. They will also convene during the period of trial implementation when interim data analysis is available, and when the final data analysis for the study is available. We will schedule three DSMB meetings a year, with the provision for cancellation should there be nothing to report. The DSMB chair will also decide if additional meetings are required in addition to these minimum meetings. Scheduled analyses will be performed by the study biostatisticians and supplied to the DSMB for review prior to each meeting. If the difference in the primary outcome (change in systolic blood pressure) between any of the intervention arms exceeds the a priori limits defined by the study biostatisticians and the DSMB, the project steering committee has the authority and obligation to consider termination of the study. The DSMB will also receive all Serious Adverse Event (SAE) Reports and may request additional information, as needed. If the DSMB chair deems that an unexpected number of SAEs have been reported they may choose to meet off cycle to assess the events and determine what action should be taken. In addition, on-site monitoring visits from a qualified research monitor (Edwin Sang) will be scheduled quarterly until data quality is deemed acceptable and then will be scheduled six monthly for the remainder of the study.

DSMB meetings are held by teleconference and or video conference as appropriate. The purpose of the first meeting was to review and discuss the DSMB charter, to provide an overview of study activities, to review and make recommendations about the protocol(s), and to determine the frequency of interim analyses and whether data will or will not be masked to identity of randomized groups.

The agenda for DSMB meetings is drafted by the ES. The agenda and meeting materials are distributed to the DSMB at least two weeks in advance of the meeting. Before each meeting, when the agenda is sent out, the Chair asks all DSMB members to state whether they have developed any new conflicts of interest since the last formal annual report to NHLBI. If a new conflict is reported, the Chair and staff determine if the conflict

limits the ability of the DSMB member to participate in the discussion. The DSMB also reviews adverse event data, other safety data, quality and completeness of study data, and enrollment data at each meeting to ensure proper trial conduct. At intervals, as noted above, the DSMB also reviews formal interim analyses of the primary end point.

It is expected that all DSMB members will attend every meeting. However, it is recognized that this may not always be possible. Quorum for voting is considered to be half the number of standing members plus one, that is, 3 members for this proposed DSMB. The DSMB may however wish to decide if particular expertise is needed within the quorum for the meeting to be valid. All standing DSMB members are voting members. The Board may also wish to decide in advance whether ad hoc members can vote.

In the case of the STRENGTHS trial, the decision as to whether to recommend early discontinuation of recruitment should be the responsibility of the DSMB based on all available evidence. Unlike trials where toxicity or inferiority of efficacy is readily demonstrable, the STRENGTHS trial is not expected to be stopped early. Safety and efficacy boundaries, however, have been created for the rare situation of unexpected benefit or harm.

Discussion of Confidential Material

DSMB meetings and calls are organized into open, closed, and executive sessions.

- During the open sessions, information is presented to the DSMB by the STRENGTHS study investigators and NHLBI staff (as appropriate), with time for discussion.

- During the closed sessions, the DSMB and NHLBI program staff will discuss confidential data from the study, including information on efficacy and safety by treatment arm. If the closed session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may elect to hold an executive session in which only the DSMB members and NHLBI Program staff are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (Robert's Rules of Order Newly Revised (11th Edition) RONR by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert). If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened at the discretion of the Chair, so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators, the STRENGTHS DCC, and NHLBI to ask questions to clarify the recommendations before adjournment. Alternatively, the DMSB's recommendations will be communicated by the Chair to the Study PI after the meeting, at the discretion of the Chair.

Reports of DSMB Deliberations

Rapid Communication: The DSMB Secretary will convey to the PI, and the NHLBI staff the immediate outcome of the DSMB meeting in regards to continuation of the study within 24 hours via personal communication, telephone or email.

Formal minutes: The DSMB Chair is responsible for the accuracy and transmission of the formal DSMB minutes within 14 days of each meeting or call. These minutes will summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The DSMB Chair may sign the minutes or indicate approval electronically via email. Then, the minutes are sent to the Principal investigator, who will be responsible for sending the document to all relevant institutional review boards, the consortium coordinating centre, and the NHLBI program and clinical trials staff. Subsequently, recommendations of the

Board are sent to the STRENGTHS primary study investigator(s); and included in the materials for the subsequent DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they will be considered final.

Reports to the DSMB
For each meeting, the ES will prepare summary reports to facilitate the oversight role of the DSMB. The DSMB should discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

Statistical Monitoring Guidelines
At the first meeting, review of the protocol will include review of the statistical analysis plan. The DSMB should discuss the adequacy of that plan. The final plan, whether part of a research protocol or separate document, will be maintained as an appendix in the formulated DSMB charter. The DSMB should discuss the statistical monitoring procedures they propose to follow, in order to guide their recommendations about termination or continuation of the trial. These procedures could include guidelines for early termination for benefit, termination for futility, and termination for safety reasons.

Protocol Violations and Protocol Deviations

Protocol deviations are accidental or unintentional changes to, or non-compliance with the research study protocol that does not increase risk or decrease benefit; or does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher, or research staff. Protocol violations on the other hand are accidental or unintentional changes to, or non-compliance with the IREC-approved protocol without prior sponsor and IREC approval. Violations generally increase risk or decrease benefit, affects the subject's rights, safety, or welfare, or the integrity of the data. In the event of a protocol deviation/violation, the PI or designee will report it to NHLBI, IREC and the DSMB as soon as possible after becoming aware, but no later than seven (7) days for protocol violations and 15 days for protocol deviations, including a 'Corrective Action Plan' for review. In addition, the RC will add the protocol deviation/violation to a log of all protocol deviations/violations, which will be maintained in the regulatory binder (Appendix 5).

Safety and Efficacy Boundaries
The DSMB should plan to conduct one major interim analysis at approximately 15 months after initiation of recruitment; the exact time being at the DSMB Chair's discretion. This is to allow for sufficient accrual of primary outcome data for a meaningful number of study participants to reasonably assess safety and efficacy of the intervention. This review will not only look at the usual safety data, but will specifically review the hypertension data in light of clinical events such as strokes, myocardial infarctions and deaths.

If an unexpectedly favorable mean change in blood pressure is noted, defined as a decrease of ≥30 mm Hg, this will be considered an unequivocal sign of benefit, and the DSMB may consider advising stopping the study for overwhelming benefit. This decision will also take into account the data regarding clinical events, especially mortality.

If an unexpectedly unfavorable mean change in blood pressure is noted, defined as an increase of ≥20 mm Hg, this will be considered as an unequivocal sign of harm and the DSMB may consider advising stopping the study for overwhelming harm. This decision will also take into account the data regarding clinical events, especially mortality.

There are no futility boundaries being set for this study given the short/intermediate term follow-up.

Should the DSMB recommend early stopping or modification of the protocol the following steps will be undertaken:

- A meeting will be held between the Principal Investigator and the DSMB to discuss the issues.
- The Principal Investigator will call a meeting with the Steering Committee, as well as the NHLBI program staff representatives. Discussions should be limited to blinded data whenever possible. This discussion should result in agreed actions based on DSMB recommendations.

Ethical Approval
The protocol for this study, data collection tools, and any subsequent amendments will receive approval from the Moi/MTRH IREC.

12. Team Roster

Table 2: STRENGTHS Team Roster

Name	Role
Dr. Constantine Akwanalo	PI
Dr. Jemima Kamano	Co-PI
Josephine Andesia Kisato	Project coordinator
Dr. Benson Njuguna	Co-investigator
Prof. Violet Naanyu	Co-investigator
Dr. Ann Mwangi	Co-investigator
Dr. Timothy Mercer	Co-investigator
Dr. Rajesh Vedanthan	Co-investigator
Dr. Sonak Pastakia	Co-investigator
Dr. Jonathan Dick	Co-investigator
Dr. Makeda Williams	Co-investigator
Dr. Gerald Bloomfield	Consultant
Tom Valente	Consultant
Eric Finkelstein	Consultant
Juliet Miheso	Research Assistant
Agneta Pkassan	Research Assistant
Eunice Njoki	Research Assistant
Monica Nyambura	Data Manager
Esther Matini Lotokho	Research Assistant
Florence Kiwunja Njulu	Research Assistant
Godfrey Kutwa	Research Assistant
Sally Asere Ekirapa	Research Assistant

Policy on oral or written presentation of results
A written policy guiding oral or written presentation of results will be developed.

13. Timeline

Table 3: Planned Enrollment by Sex

Targeted/Planned Enrollment		
Males	Females	Total
990	660	1650

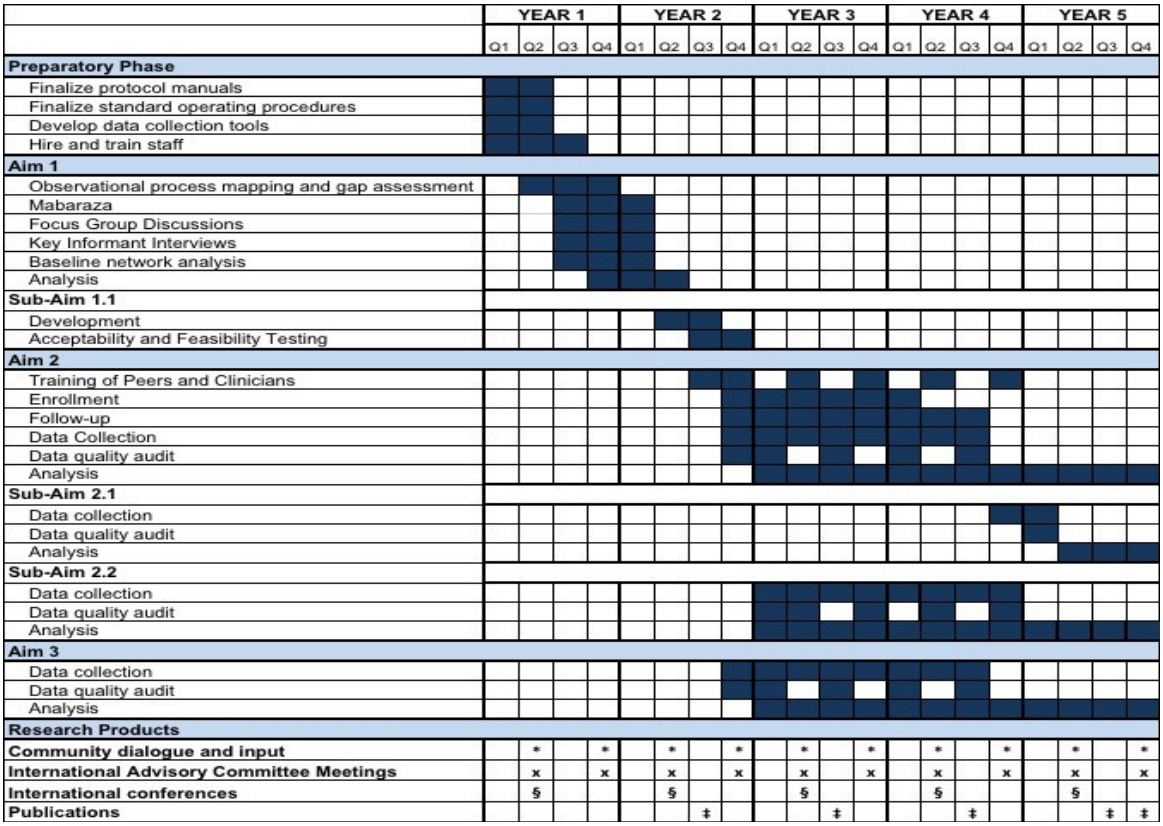

Figure 5: Timeline for overall STRENGTHS Study

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15. Appendix

Appendix 1: Screening for eligibility tool

STRENGTHS
SCREENING/ELIGIBILITY TOOL
Inclusion Criteria

	Questions	Response	Code
QA-1	Participant ID	Participant ID	__ __ __ __ __
QA-2	Encounter Date	Date of Encounter	__ __ / __ __ / __ __ __ __ Day/Month/Year
QA-3	Name of the Interviewer	Kisato J. Miheso J. Parklea A. Mwangi Njoki E. Njuguna B. Akwanalo C. Kamano J. Vedanthan R. Other.	1 2 3 4 5 6 7 8 _____
QA-4	Is patient at least 18 years of age or older?	Yes No **[Do no continue-ineligible]**	1 0
QA-5	*Enrolled in AMPATH CDM program with hypertension.*	Yes No	1 2

If referred up, confirm (must meet at least one of the following criteria):

	Questions	Response	Code
QB-1	Uncontrolled blood pressure (SBP ≥ 140 or DBP ≥ 90) on 3 or more anti-hypertensive medication?	Yes No	1 0
QB-2	Have signs or symptoms of end-organ damage (dyspnoea on exertion, leg edema, reduced urine output, focal weakness)	Yes No [Go to QB-4]	1 0
QB-3	**[If QB-2=1]** Please state the sign(s) or symptom(s) of end-organ damage **(check all that apply)**:	Dyspnea on Exertion Leg Edema Reduced Urine Output Focal Weakness	1 2 3 4
QB-4	Have suspected secondary causes of hypertension (age <35 years, HIV, or	Yes No [Go to QB-6]	1 0

	pregnancy)?		
QB-5	[If QB-4=1] Please state the suspected secondary causes **(check all that apply)**:	Ag <35 years HIV Pregnancy	1 2 3
QB-6	Any other concerning condition that the clinician suspects to be attributable to hypertension for which they would seek a higher level of care	Yes No	1 0
QB-7	Referral up criteria confirmed (if yes to at least one of the previous questions).	Yes No	1 0
Go to QD-1			

If referred down, confirm (must meet at least one of the following criteria):

	Questions	Response	Code
QC-1	Patient has stable, uncomplicated hypertension, defined as controlled BP (SBP <140 and DBP < 90) for 3 or more consecutive visits and has no evidence of new end-organ damage	Yes No	1 0
QC-2	The treating clinician recommends care at a lower level	Yes No	1 0
QC-3	If Q2= 0, explain clinician's reason.	Clinician's reason	_____
QC-4	Referral down confirmed (if yes to at least one of the questions).	Yes No	1 0

Exclusion Criteria (if patient meets any of the following):

	Questions	Response	Code
QD-1	Patient has an acute illness requiring immediate medical attention?	Yes No	1 0

QD-2	End stage disease?	Yes No	1 0
QD-3	Terminal illness?	Yes No	1 0
QD-4	Inability to provide informed consent (determined by interviewer)?	Yes No	1 0
QD-5	[If QD-4=Yes] Please explain.	Explain	_____
QD-6	Did the participant answer ALL of the following questions correctly? 1. Who is the current president? 2. Where are we located?	Yes No	1 0
QD-7	Eligible?	Eligible Not Eligible	1 0
QD-8	Would you be willing to join the STRENGTHS study?	Yes No	1 0
QD-9	Please give reason for declining.	Reason Declined	_____
QD-10	Consent?	Yes No	1 0

Appendix 2: Consent Form STRENGTHS

INFORMED CONSENT FOR STRENGTHS TRIAL

IREC Study ID #: 0001936 **Participant ID #: _____**

Consenting start time: _____

Principal Investigators: Constantine Akwanalo and Jemimah Kamano

Protocol Title: Strengthening Referral Networks for Management of Hypertension across the Health Systems (STRENGTHS)

Purpose of this Research Study

The purpose of this study is to find ways to improve success of referrals for hypertension care in rural Kenya. AMPATH and the Kenya Ministry of Health have implemented a referral network for the care of hypertensive patients in this area across different levels (that is, from dispensary, to health center, sub-county, county and national referral hospitals). AMPATH is planning to evaluate the impact of health information technology (health IT) combined with peer support (trained patients with hypertension) on successful referral for hypertension care and control of blood pressure among patients. We therefore plan to compare the impact of the combined intervention (that is, health IT and peer support) on blood pressure control versus the usual standard clinical care. The results of this study are not only designed to improve hypertension care in Kenya, but will also be applicable to the management of other chronic diseases in Kenya and other developing countries.

You are eligible to take part in this research study because you are hypertensive, enrolled in the AMPATH Chronic Disease Management Program and have been referred to another health facility for further care.

Duration of Participation and Number of People Expected to Participate
Participation Duration: One year
Anticipated Number of Subjects: 1600

Description of Procedure
If you agree to participate in this research study, the following information explains what may be involved.

To evaluate the impact of combining health IT and peer support on the quality of hypertension care, we are dividing the community into two random groups, one with usual clinical care and the other with our referral support intervention (combined health IT with peer support). Depending on the community unit you live in, you might be approached to receive our referral support intervention to help direct your referrals, or have your referral conducted as per the usual care (with no referral support intervention). If you receive the referral support intervention, a peer (patient with hypertension who is trained in supporting other patients with hypertension) will sit with you and clarify any questions you may have about your referral, and provide education and counseling about hypertension. In addition, in planning for your referral visit, the peer will assist you to plan e.g. provide you with information of anticipated costs for the referral, and help with booking an appointment in the facility you've been referred to. On the day of your visit, a different peer stationed at the receiving facility will be waiting to receive you and assist you to navigate through the facility. At the end of your referral visit, the peer will again clarify any questions you may have. Throughout your participation in the study, the peer may call you or even visit you at home to offer you furthur support for your referral.

The clinicians and the services offered will be the same regardless of the community you are coming from. The fees paid, which have been agreed upon by AMPATH and the Ministry of Health, will also remain the same.

At the beginning of the study we will ask you questions concerning your high blood pressure, medications you take, diet, physical activity level and other lifestyle related questions. We will measure your blood pressure and conduct blood tests to measure your lipid ("fat in blood") levels, and how well your kidneys are working using a test called the creatinine test. To do this, we will need to prick you to withdraw blood using a small needle. About 10 mls of blood will be taken and fed into a portable machine that can determine the results of these tests, or transported back to a health facility laboratory for testing. All the blood test results will be immediately made available to you and we will share the results with your clinician. Taken together, the tests conducted will help us determine your risk for future complications of hypertension such as heart disease. We also wish to study the costs and expenses related to your medical care, to see if there is any difference in costs in the two different groups, therefore, we will ask you questions regarding how much you spend for your hypertension care.

We will repeat the above procedures at the end of the one-year period in which you'll be in the study, so that we can see if there has been any change in these results. The one-year results will also be shared immediately with you and your clinician. If we cannot find you at the end of the 1-year period, we will contact you or your relative by phone.

Confidentiality of Study Data
We will not use your name or any other identifying information when we use this information that you are giving us. The only people who will know that you are a research participant are members of the research team who are trained to keep your information confidential and if appropriate, your health care providers and study clinical monitor. No individual identifying information about you will be disclosed to others, except if required by law.

Study records will be stored in locked cabinets in a locked room. Only the study personnel will have access to the information. All computerized information will be protected by access codes known only to the lead researcher and certain designated staff members.

Potential Benefits
The referral support intervention might lead to more successful referral completion for you, and improved health. In addition, the information gathered during this research study will help AMPATH improve the implementation of this program. You, your family, and your community may therefore benefit from this research.

Potential Risks or Discomforts
We will only be collecting personal health information that is a routine part of clinical care, as well as the cost information. This information will be shared only with your clinicians, in order to provide you the best clinical care possible.

Risks associated with blood pressure testing are minimal and may include minor pain discomfort, and swelling at the location of the needle prick, small risk of dizziness, light headedness, and fainting. The risk is however no more than what you may experience during your usual routine clinical care visit.

Voluntary Participation and Right to Discontinuation
It is completely voluntary for you to take part in this study. If you choose to take part, you can refuse to answer any question or ask us to stop at any time with no penalty. This will not affect in any manner your ability to receive medical care at any health facility (private/public), or to receive any benefits to which you are otherwise entitled.

Compensation
Participants will get transport reimbursement at the 6 month and 12 month follow up visit, however, the initial visit, or any costs associated with completing a referral or any usual clinical care will not be provided. A snack will be provided during the consenting and interview procedures as these will take away time from you.

Future Contact
We would like to follow you up after six and twelve months. We therefore request for your permission to contact you or any other person (if unavailable) as provided in the demographic data form.

Disclosure of Financial Interests
Funding for conducting this research is provided by the National Institutes of Health, USA, and Grant number: U01HL138636. There are no financial interests to disclose.

Contact Information:
In case of any questions/complaints regarding this study, please contact:
Dr. Constantine Akwanalo
Moi University College of Health Sciences
Eldoret, Kenya
cakwanalo@gmail.com
0722862968

Is it okay for you to participate in this research study?

PARTICIPANT'S INFORMED CONSENT
I Mr/Mrs/Ms/Dr……..have read/ have had the document read to me, all my questions have been answered and I have understood the information contained in the consent form above. I agree to voluntarily take part in the study. I acknowledge receipt of a copy of the informed consent statement.
PARTICIPANT'S SIGNATURE:_____Date_____
(Must be dated by the participant if literate)

NAME OF WITNESS: ……
SIGNATURE OF WITNESS: _____Date: _____
(Impartial witness) (Must be dated by witness)
NAME OF PERSON OBTAINING CONSENT: _____
SIGNATURE OF PERSON OBTAINING CONSENT:_____Date: _____
Consenting stop time: _____

Appendix 3: Process Evaluation Protocol

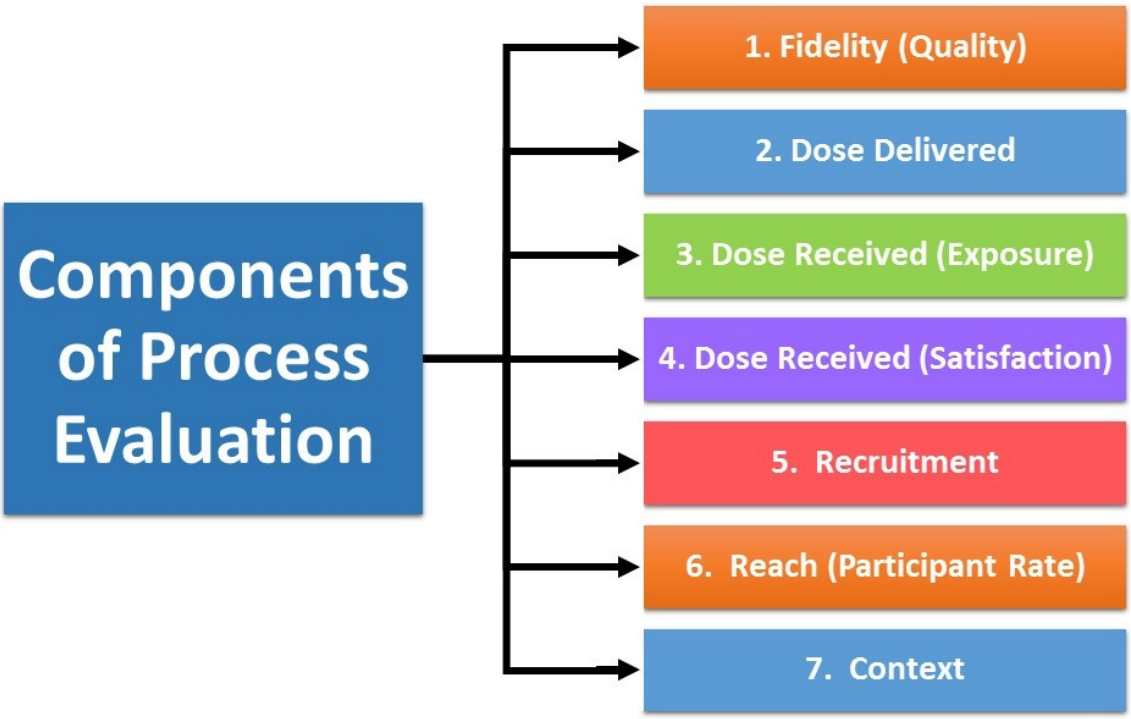
STRENGTHS Process Evaluation Protocol

Last Modified: October 9, 2019

Overview of STRENGTHS Process Evaluation

The purpose of the process evaluation is to identify and correct problems in study implementation during the trial as well as help explain the results of the trial after the fact. The process evaluation for the STRENGTHS project is based on the Saunders framework[1] and will consist of several components: fidelity (quality), dose delivered (completeness), dose received (exposure), dose received (satisfaction), recruitment, reach (participation rate), and context, as demonstrated in the graphic below.

[1] Saunders RP, Evans MH, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. *Health Promotion Practice.* 2005; Apr; 6(2): 134-47.



Each process evaluation component will be assessed using several data collection tools. The protocol below goes over each of the individual data collection tools in detail.

A Process Evaluation REDCAP will be utilized for the management of all quantitative data. Data will be entered by research assistants, verified by the research coordinators and data manager, and analyzed by the statistics team. Qualitative data will be transcribed by the research assistants and analyzed by the research coordinators using NVivo software.

Acronyms:

BP – Blood Pressure

CDM – Chronic Disease Management

FGD – Focus Group Discussions

HIT – Health Information Technology

KII – Key Informant Interviews

PN – Peer Navigators

RA – Research Assistant

SOP – Standard Operating Procedures

UC – Usual Care

1. Fidelity (Quality)

Aim: To assess how well the trial was implemented as planned
Specific aims: To assess the fidelity of a) data collection and entry and b) the intervention delivery

a) Fidelity of Data Collection and Entry:

Data Collection Observation

Participants:
All members of the research staff that will be collecting data from participants will be observed.

Methods:
A study investigator and the research coordinator will observe research staff at the beginning of the study or at the point of hiring (for new staff). Additional observation will be conducted at 3 and 12 months if determined to be needed. The principal investigator and research coordinator will be provided with a checklist of expected behaviors and actions and will check off items as they are completed. The checklist items will be based on the study protocol procedures. The checklist will assess:
Measurement taking: BP, height, weight, waist circumference, using point of care machine (fasting blood sugar, lipid profile)
Survey conduct and connection to participant during survey administration (observe each surveyor 3-4 times and give feedback). Includes Costing Questionnaire and Social Network Survey.
Informed consent procedure (includes eligibility and consent forms, proper use of REDCap, and study explanation)

Outcomes and Analysis:
The statistics team will summarize adherence for each checklist item, and each research staff member's score will be calculated as percent completion. The principal investigator and research coordinator will identify problem areas and provide individual feedback and follow-up training as necessary.

Data Entry

Participants:
All members of the research staff that will be entering data from participants at baseline and/or 3 or 12 months will be observed.

Methods:
The data manager and research coordinator will ensure that the following data entry checks are being utilized per the Data Management SOP: double data entry of paper forms for critical fields built into the data management system and out of range checks built into the data management system.

Outcomes and Analysis:
The data manager and research coordinator will determine the adherence to the Data Management SOP to assess if the double data entry and out of range checks were implemented as intended. Data manager will utilize quality control feature of REDCAP to determine how many validation errors are made per research assistant, as defined in the Data Management SOP.

b) Fidelity of Intervention Delivery:

Field Observation:

Participants:
All PNs and clinicians enrolled in the study will be observed.

Methods:
Trained research staff will observe PN actions and interactions by month 3 of the intervention during a site visit. The research staff will be provided with a checklist of expected behaviors and actions and will check off actions as they are completed. The checklist items will be based on the PN guides and designed to assess whether or not their role is being implemented as intended. If needed based on performance (on a case-by-case basis based on results reported on the field observation checklist), additional field observation can be conducted subsequently.

Trained research staff will also observe clinician actions and interactions by month 3 of the intervention during a site visit. If needed based on performance, additional field observation can be conducted subsequently. The research staff will be provided with a checklist of expected behaviors and actions and will check off actions as they are completed. The checklist items will be based on the clinician guides and designed to assess whether or not their role is being implemented as intended.

Outcomes and Analysis:
The statistics team will summarize adherence for each checklist item, and each PN's score will be calculated as percent completion. Adherence will be compared by arm (as applicable), age, gender, and geographical region. The research staff will identify problem areas based on items not conducted (as per the field observation checklist) and will provide individual feedback and follow-up training as necessary. Should certain PNs not meet the expectations after additional training, they will be replaced with another PN from the same community unit.

Written Test:

Participants:
Every PN will be given written tests.

Methods:
Separate written tests will be given to the PNs assessing knowledge of hypertension care, understanding of the referral system, as well as psychosocial support and patient communication

The test will be translated into Kiswahili and will be administered at baseline (following training) and 6 months.

Outcomes and Analysis:
The statistics team will summarize the results from the written test and do comparisons by groups (geographical region, age, gender, and intervention arm). PN ID numbers will be recorded on the test form to link the baseline and follow-up tests. Each PN's score will be calculated as percent completion. The research staff will identify problem areas and provide individual feedback and follow-up training as necessary based on preliminary analysis of the baseline test. A score lower than 80% will be flagged for review by the principal investigator and/or the research coordinator, and will be evaluated on a case-by-case basis to determine if additional training/feedback is necessary.

Focus Group Discussions:

Participants:
FGDs will be conducted amongst consenting trial participants who have been retained in the trial, participants who dropped out of the trial (based on the clinical definition of a drop-out as someone who has not returned for care in 3 months since the last scheduled appointment), and among PNs. Two clusters from the intervention arm and two clusters in the UC arm will be randomly selected in which one FGD will

be conducted in each consisting of 8-10 randomly selected participants from the intervention arm (for a total of 4 FGDs). UC participants will be recruited from different health facilities in the applicable cluster.

Retained Participants				**Participants that dropped out**		**Peer Navigator**
Cluster 1	Cluster 2	Cluster 3	Cluster 4	All Clusters	All Clusters	All Clusters
HIT + peer support	HIT + peer support	UC	UC	HIT + peer support	UC	HIT + peer support

Method:
FGDs will be conducted at approximately 8 months. Data collected through focus group discussions will be used to evaluate fidelity as well as other components of the framework as noted throughout this protocol. A summary of all data collected through FGDs is noted below.
Participant FGD will:

- Assess participant perceptions of the different intervention components, including the PN and rural clinician activities
- Determine if the intervention is acceptable to participants
- Identify barriers to use and points of successful use of the intervention
- Elicit suggestions from participants about improving the intervention effectiveness

PN FGD will:

- Assess if they think peer navigation is helpful for participant care
- Assess perceptions of participant engagement
- Determine if the intervention is acceptable to the providers
- Identify barriers to use and points of successful use of the intervention
- Ascertain if interventions are meeting trial arms and objectives
- Elicit suggestion for improvement

Outcomes and Analysis:
Content analysis of the FGD data from transcripts of the audio-recordings and notes taken by facilitators during the discussion will be performed using NVivo software. For the participant FGD, the following a priori codes will be used: perceptions of PN and rural physicians, perceptions of intervention activities, importance of hypertension care, importance of referral pathways, and quality of referral services. For the PN FGD, the following a priori codes will be used: perceptions and concerns related to HIT and peer support, cognitive issues around patient interaction (perceived benefit, participant receptivity), emotional elements (frustrations, fears, expectations), and the impact of gender dynamics. Significant inductive (emerging) codes will be identified.

Semi-structured interviews with clinicians

Participants:
Approximately 18 clinicians will be interviewed at 8 months (at least one from the primary and secondary level from each cluster, and at least 2 from the tertiary level; Moi Teaching and Referral Hospital)

Methods:
Trained research staff will conduct semi-structured interviews with the rural clinicians using a structured question guide with the following goals:

- Assess if they think the intervention (use of HIT and peer support) is helpful for participant care
- Determine if the intervention is acceptable to the providers

- Identify barriers to use and points of successful use of the intervention
- Ascertain if interventions are meeting trial arms and objectives
- Elicit suggestion for improvement
- Assess how HIT and peer support impacts patient-clinic interaction

Outcomes and Analysis:
Content analysis of the interviews from transcripts of the audio-recordings and notes taken by interviewers will be performed using NVivo software. The following a priori codes will be used: perceptions and concerns related to managing the HIT and peer support, cognitive issues around intervention (perceived benefit, participant receptivity), emotional elements (frustrations, fears, expectations), and impact of gender dynamics. Significant inductive (emerging) codes will be identified.

2. Dose Delivered (Completeness)

Aim: To determine the number of units of each intervention delivered and if they included the necessary components
Specific aims: To determine if the referral services were provided to participants and in accordance with the components as outlined in the training manuals

Participant Self-Reports

Methods:
At the conclusion of 6-month and 12-month visits, 5 randomly selected participants will fill out a brief checklist of tasks completed during the meeting. The checklist will include items assessing PN referral services provided during the visit. These sheets, which will be available in both English and Swahili, will be collected approximately every 3 months when research staff conduct site visits.

Outcomes and Analysis:
The statistics team will summarize task completion by individual facility and by arm over the 12 months.

3. Dose Received (Exposure)

Aim: To assess to what extent participants were actively engaged with and receptive to the intervention, including initial use and continued use.
Specific aims: To assess participant engagement with the intervention as well as UC, both from the participant and PN perspectives.

Focus Group Discussions
Conducted as outlined in 1. b) III.

Semi-structured interviews with rural clinicians
Conducted as outlined in 1. b) IV.

Field Observation
Conducted as outlined in Section 1. B) I.

Outcomes and Analysis:
Descriptive statistics will be performed with stratified analysis by relevant demographic characteristics as appropriate.

4. Dose Received (Satisfaction)

Aim: To assess the level of participant and provider satisfaction both with the intervention and with their interactions with project staff
Specific aims: To assess the level of participant and provider satisfaction with the implementation of the intervention, as well as UC.

Focus Group Discussions

Conducted as outlined in Section 3a) with focus on participant and provider satisfaction with the intervention components

Semi-structured interviews with rural clinicians

Conducted as outlined in Section 3b) with focus on provider satisfaction with the intervention components.

5. Reach (participation rate)

Aim: To determine what percentage of the enrolled participants that participated in the intervention.
Specific Aim: To determine the percentage of patients being referred who met with both the PN at their referring facility, as well as the PN at their receiving facility. This will thereby assess retention. Barriers to participation will also be assessed.

Clinic Attendance in Usual Care

Participants:
Every study participant in the UC arm.

Methods:
Every study participant in the UC arm will have their clinical attendance data extracted. Clinic attendance is defined as the completion of a CDM form. The data team will extract dates of CDM clinic attendance from the AMRS for each study participant at 12 months.

Outcomes and Analysis:
The statistics team will summarize the number of clinic appointments over 12 months by arm.

Peer Navigator Encounter in Intervention Arm

Participants:
All patient encounter data will also be extracted from the research database for each participant in the intervention. A patient encounter is defined as the completion of a patient encounter form by the PN.

Methods:
Every study participant in the intervention arm (receiving HIT and peer support) will also have their encounter data extracted as defined above.

Outcomes and Analysis:
The statistics team will summarize the number of encounters over 12 months by arm.

Focus Group Discussions

Conducted as outlined in Section 3a). Specifically, the drop-out focus groups will help assess why certain participants stopped participating.

6. Recruitment

Aim: To assess what procedures were used to attract participants and what percentage of eligible participants were enrolled out of the total number recorded as eligible during screening.
Specific Aim: To determine which enrollment procedures were utilized to screen patients eligible for enrollment, and monitor enrollment procedures.

Field built into eligibility form

Participants:
Research staff involved in enrolling participants will be prompted by the screening and eligibility form on the data management software

Methods:
The screening and eligibility form on the project REDCap will prompt research staff to type in a reason when eligible participants choose not to enroll. For patients that do enroll, research staff will indicate which enrollment procedures were utilized. The data management program will also log the attempts to contact and enroll participants and the statuses of these attempts through the scheduling module.

Outcomes and Analysis:
Reports generated by the data management system will be used to evaluate recruitment strategies and improve as necessary. In order to determine what percentage of eligible participants were enrolled, we will first determine how many participants were eligible from each recruitment pathway. From this, the data team can calculate what percentage of eligible patients were enrolled per pathway and in total.

Semi-structured interviews with research staff

Participants:
Key members of the research staff in Kenya who were most directly responsible for STRENGTHS participant recruitment will be interviewed at 6 months.

Methods:
Trained research staff who were not directly involved with participant recruitment will conduct semi-structured interviews with the research staff responsible for recruitment using a structured question guide with the following goals:

- Determine what planned and actual recruitment procedures were used to recruit participants
- Identify barriers in recruitment and successful strategies

Outcomes and Analysis:
A content analysis of the interviews from transcripts of the audio-recordings and notes taken by interviewers will be performed using NVivo software. The following a priori codes will be used: recruitment procedures, barriers in recruitment, successful recruitment strategies. Significant inductive (emerging) codes will be identified.

7. Context

Aim: To assess the aspects of the environment that may influence intervention implementation or study outcomes, including contamination or the extent to which the control group was exposed to the program.
Specific aim: To assess the barriers and facilitators to the two intervention arms, from the participant, provider, and staff perspectives

a) Focus Group Discussions:
Conducted as outlined in Section 3a) with focus on barriers and facilitators to implementing the intervention.

b) Semi-structured interviews with clinicians and research staff:

Conducted as outlined in Sections 3b) and 6b) with focus on barriers and facilitators to implementing the intervention.

Appendix 4: Adverse Event and Serious Adverse Event Reporting Form

STRENGTHS
ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

NOTE: Complete this report within 24 hours of knowledge of an adverse event occurring or worsening after consent. This report must be filled together/reviewed by the principal investigator or delegated co-investigator. All SAEs will require expedited reporting by the PI to the study's DSMB, IREC/IRB, and NHLBI. An expedited report of an SAE will be submitted by email and must be reported to the DSMB, IREC/IRB and the NHLBI within 24 hours of the event being reported to the Investigator. The expedited report will be followed by a detailed, written AE/SAE report as soon as possible.

Causal Relationship

The assessment of the causal relationship is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on whether there was a "reasonable causal relationship" to the study interventions. An assessment of "No" would include the existence of a clear alternative explanation or non-plausibility. An assessment of "Yes" indicates that there is a reasonable suspicion that the event is associated with the subject's participation in the study. Factors to be considered in assessing the relationship of the event to study treatment include:

- The temporal sequence from study intervention procedures: The event should occur after the intervention is delivered. The length of time from exposure to event should be evaluated in the clinical context of the event
- Recovery on intervention discontinuation, recurrence on intervention re-introduction: Participant's response after discontinuation should be considered in the view of the usual clinical course of the event in question
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have
- Concomitant medication or treatment: Drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them may be suspected to cause the event in question

Alternative possible explanations

- **Concomitant disease:** any illness participant has at time of entering the study, excluding the indication for study intervention
- **Concomitant drug:** any medication the participant was receiving at time of event onset
- **Intercurrent disease:** any illness the participant may develop during the study
- **Underlying disease:** the indication the intervention is being tested for

SECTION A – INTRODUCTION

	Question	Response	Code
QA-1	Participant ID	Participant ID	_ _ _ _ _
QA-2	Start Date of Event	Start Date Don't Know	_ _ / _ _ / _ _ _ _ Day/Month/Year 99
QA-3	End Date of Event	Stop Date Ongoing Don't Know	_ _ / _ _ / _ _ _ _ Day/Month/Year 88 99
QA-3	Date and time investigator became aware of this event	Date Time (in 12-hr clock)	_ _ / _ _ / _ _ _ _ Day/Month/Year _ _ : _ _ hr—min. pm/am
QA-4	Does this event associated with any of the following **seriousness criteria**? (Select all that are appropriate)	Results in death Is life threatening Results in hospitalisation or prolongation of hospitalisation Results in persistent or significant disability or capacity (If any of the above are selected, **Go to section B**) None of the above (**Go to section c**)	1 2 3 4 5

SECTION B – SERIOUS ADVERSE EVENT

	Question	Response	Code
QB-1	Serious Adverse Event, please fill out the details of the event and give specific diagnosis if possible e.g. heart failure, death etc		
QB-2	What was the <u>intensity</u> of the SAE	Mild (transient in nature and not interfering with normal activities) No [Sufficiently discomforting to interfere with normal activities] Severe [prevents normal activities] Don't know	1 2 3 99
QB-3	Is there a reasonable causal relationship to any of the study interventions? (see definitions on page 1)	Yes No	1 2
QB-4	What action was taken with the study intervention?	Study intervention withdrawn (Go to QB-5) Study intervention temporary interrupted (Go to QB-5) No action (Go to QB-7)	1 2 3
QB-5	Did event disappear after stopping study interventions?	Yes No Unknown	1 2 99
QB-6	Did event reappear after reintroducing study interventions?	Yes No Study interventions not reintroduced Unknown	1 2 3 99
QB-7	Are there any alternative possible explanations for this event? (see definitions on page 1)	Concomitant disease Concomitant drug Intercurrent disease Underlying disease Unknown	1 2 3 4 99
QB-8	What was the outcome of this event?	Recovered/Resolved Not Recovered/Not Resolved Recovering/Resolving Fatal Recovered/resolved with sequelae Unknown	1 2 3 4 5 99

SECTION C – NON-SERIOUS ADVERSE EVENT

	Question	Response	Code

QC-1	Non-Serious Adverse Event, please fill out the details of the event and give specific diagnosis if possible e.g. heart failure, death etc		
QC-2	What was the intensity of the non-serious AE	Mild (transient in nature and not interfering with normal activities) No [Sufficiently discomforting to interfere with normal activities] Severe [prevents normal activities] Don't know	1 2 3 99
QC-3	Is there a reasonable causal relationship to any of the study interventions? (see definitions on page 1)	Yes No	1 2
QC-4	What action was taken with the study intervention?	Study intervention withdrawn (Go to QC-5) Study intervention temporary interrupted (Go to QC-5) No action (Go to QC-7)	1 2 3
QC-5	Did event disappear after stopping study interventions?	Yes No Unknown	1 2 99
QC-6	Did event reappear after reintroducing study interventions?	Yes No Study interventions not reintroduced Unknown	1 2 3 99
QC-7	Are there any alternative possible explanations for this event? (see definitions on page 1)	Concomitant disease Concomitant drug Intercurrent disease Underlying disease Unknown	1 2 3 4 99
QC-8	What was the outcome of this event?	Recovered/Resolved Not Recovered/Not Resolved Recovering/Resolving Recovered/resolved with sequelae Unknown	1 2 3 4 99

SECTION D – CONCLUSION

	Question	Response	Code
QD-1	Name of the Interviewer/Research Assistant	_____	
QD-2	Date of documentation		__ __ / __ __ / __ __ __ __ Day/Month/Year
QD-3	Name of the Investigator reviewing this information	_____	
QD-4	Date of Investigator review		__ __ / __ __ / __ __ __ __ Day/Month/Year

Appendix 5: Protocol Deviation/Violation Log

Protocol Deviation/Violation Log

Description of Protocol Deviation:	**Deviation Category***	**Deviation Code****	**Date Deviation Occurred:** (dd/mm/yyyy)	**Date IREC/ IRB Notified**	**Principal Investigator's Signature**	**Date Signed** (dd/mm/yyyy)

***DEVIATION CATEGORIES:**

A. Safety
B. Informed Consent
C. Eligibility
D. Protocol implementation
E. Other, specify in log

**DEVIATION CODES: Numbers listed by the sample protocol deviations

Safety (Category A)

1. Not reporting an SAE within 24 hours
2. Laboratory tests not done
3. AE/SAE is not reported to IRB
4. Other, specify in log

Informed Consent (Category B)

5. Failure to obtain informed consent
6. Consent form used was not current IRB-approved version
7. Consent form does not include updates or information required by IRB
8. Consent form missing
9. Consent form not signed and dated by participant
10. Consent form does not contain all required signatures
11. Other, specify in log

Eligibility (Category C)

12. Participant did not meet eligibility criterion
13. Randomization of an ineligible participant
14. Participant randomized prior to completing Baseline Assessment, etc.
15. Randomization and/or treatment of participant prior to IRB approval of protocol
16. Other, specify in log

Protocol implementation (Category D)

17. Failure to keep IRB approval up to date
18. Participant receives wrong treatment
19. Participant seen outside visit window
20. Use of unallowable concomitant treatments
21. Prescribed dosing outside protocol guidelines
22. Missed assessment
23. Missed visit
24. Other, specify in log