Determining the optimal diagnostic and risk stratification approaches for people with hypertension in two rural populations in Kenya and The Gambia.

(IHCoR-Africa Work Package 2)

Protocol version 1.1 dated 25 January 2023

Lay Summary

Formal Title:
Determining the optimal diagnostic and risk stratification approaches for people with hypertension in two rural populations in Kenya and The Gambia

Lay Title:
Identification and management of high blood pressure in rural Africa

What is the problem/background?
Many people live with high blood pressure (HBP) in SSA, the region of Africa south of the Sahara Desert. In this region, the proportion of people with HBP is amongst the highest in the world. In SSA, HBP occurs in younger individuals. Few individuals with HBP get treated resulting in significant medical complications and premature death. This is a serious health concern particularly in SSA where there is little knowledge about risk factors or treatment for this condition.

The high disease burden from HBP in rural SSA is likely to be due to multiple factors including lack of clear symptoms; restricted access to healthcare; and competing demands on time which may prevent people from going to clinics and seeking care. One suggested approach to improve the management of people with HBP in rural SSA is to use a community-centred approach, where care is more actively promoted and brought into the community to remove obstacles in accessing it.

The project *Improving Hypertension Control in Rural Sub-Saharan Africa* (IHCoR-Africa) of which this study is part of, investigates ways to improve care for people living with HBP in rural Kenya and The Gambia by working together with community health workers.

The project consists of three work packages (WPs). WP1 focusses on understanding the existing health care structures to detect, treat and control HBP, while WP2 (this study) investigates ways to better identify people with HBP and related health complications. Moreover, WP2 will determine which people are most at risk to have HBP and associated medical complications. WP3 will use the findings of WP1 and WP2 to develop a community-centred programme to better help people suffering from HBP in rural SSA.

What questions are we trying to answer?
Main objective:
How can we improve the way community health workers identify who to refer for treatment of HBP.
Sub Questions:

1. How accurate are three alternative blood pressure measurement methods performed by community health workers in identifying people with HBP in rural SSA, compared to the best available method?
2. Among those people with HBP, how many have developed damage to some of their organs (kidneys, heart and eyes) caused by the HBP?
3. What are risk factors for developing HBP (for example body mass index or family history)?
4. Can simple devices and measurement tools accurately determine who has organ damage?
5. What is the most cost-effective way to identify who to treat among people with HBP?

Where is the study taking place, how many people does it involve and how are they selected?

The study will take place across two rural sites: in East Africa (Kilifi, Kenya), and in West Africa (Kiang West, The Gambia). The study will involve 1250 participants in total, divided equally over the two study areas. We will select from both sites an age-stratified random sample of 625 participants aged ≥30 years from the population registers of Kilifi and Kiang West. Those who fit the inclusion criteria (being able to consent, ≥30 years at date of recruitment, able to perform the study procedures, not pregnant/lactating) and provide written informed consent will join the study.

What does the study involve for those who are in it?
After joining the study, participants will be asked general questions about their health for example, age, weight, height, level of physical activity and their diet. Additionally, they will undergo simple physical assessment of their health status.

During a two-week period, they will undergo four different methods of blood pressure measurement in a random order. All these measurements will be conducted in the participant's home. These measurements are:

- Attended automated blood pressure measurement (aABPM). Here, a community health worker will conduct a blood pressure measurement using an automated machine and record the readings.
- Unattended automated blood pressure measurement (uABPM). Here, an automated blood pressure machine will be used to record a participant's blood pressure without having the community health worker present in the room while the measurements are being conducted.
- Home Blood Pressure Measurement (HBPM). Here, the participant will be asked to record their blood pressure every morning and evening for 7 consecutive days with a blood pressure machine they will be given.
- 24-hour ambulatory blood pressure monitoring (24-hr ABPM). Here, a blood pressure machine will be put on the participant arm to record the participant's blood pressure continuously over 24 hours.

After completion of the blood pressure measurements, participants will be asked a few questions regarding their experience using the four methods.
The study team will review the measurements recorded for each participant after the two-week period and determine whether they suffer from HBP. These results will be fed-back to the participants after all measurements have been performed.

All participants will then be invited to the study clinic for further assessments to determine whether they have organ damage. Participants will be asked questions about their health status. They will also have assessments to detect organ damage in the eyes, kidneys and the heart will be done. These will include cameras to scan the eyes and sensors placed on your body to check your heart function, including a blood pressure cuff. These assessments will include collecting a 15-millilitre sample of blood (about 3 teaspoons) and a urine sample. In addition, aABPM and uABPM measurements will be repeated to assess the reliability of the home aABPM and uABPM measurements compared to those done at the clinic.

We will also perform additional simple measurements among all participants to compare these simple tools for identifying organ damage with the standard techniques used in the preceding set of measurements. These simple tools include a smartphone camera to scan your eyes, sensors placed on your chest to examine your heart, and a blood pressure cuff. We will also use some of the blood we have taken in a handheld blood test machine.

All the study visits and assessment for each participant will be completed within a four-week period.

What are the benefits and risks/costs of the study for those involved?

Benefits:

The participants will get feedback about their health status after the measurements are performed. Participants will also undergo additional tests to identify any organ damage. All participants with HBP will be referred to the appropriate health centres for further management.

The study will benefit the community by increasing the knowledge and capacity of local health workers to better identify and refer patients with HBP for appropriate management. Consequently, individuals suffering from HBP in rural areas will receive better care.

Risks/costs:

In general, the research activities are low risk.

Participants will be invited to the study clinic for further assessment. During this visit, they will incur transport costs and lose time they would otherwise spend working. The study will reimburse them their exact fare spent and give them an out-of-pocket reimbursement of 500 Kenyan shillings (Kshs) for each visit for those in Kenya and 250 Gambian Dalasi for those in The Gambia in line with MRCG at LSHTM policy.

The collection of blood (total of 15 ml) is safe and will not cause any harm but might cause a little temporary discomfort and possibly some bruising of the skin. There is also a small risk of local infection at the site of the blood draw, which will be minimized by use of sterile equipment and trained clinical staff.

The study activities do require time and effort from the participant as measurements take place on multiple days and the participant must perform some measurements by themselves. However, these home measurements will take less than 10 minutes each day and will not hinder the participant from performing their daily duties.

The 24-hr ABPM procedure does not do any harm to the participant but having to carry a device on the body for 24 hours might be uncomfortable and inconvenient. The device comes with a small bag to make carrying the machine as convenient as possible for the participant.

How will the study benefit society?

This study is part of the wider IHCoR-Africa study. In this study an evidence-based, context specific, and community-centred intervention will be developed to manage high blood pressure in rural SSA. The work in this protocol will deliver the strongest evidence to date about different diagnostic approaches for high blood pressure in rural SSA, a unique understanding of the frequency and characteristics of organ damage related to high blood pressure in this population, and a robust assessment of the role of innovative, simple point-of-care devices to manage high blood pressure in rural SSA. In addition, it will provide new evidence of high blood pressure risk factors in rural SSA. Ultimately, the impact of this study (together with other activities of the IHCoR-Africa study) is expected to improve the outcome of people living with high blood pressure in rural SSA.

When does the study start and finish? Research activities will start upon receipt of ethical and regulatory clearance from the relevant institutions and organisations in Kenya, The Gambia and the UK. This is planned for March 2023. Participant recruitment, data collection and analysis are projected to last for 13 months and complete in April 2024. Dissemination activities will run until the conclusion of the wider IHCoR-Africa project in January 2026.

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Figures and Tables

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Abbreviations

24-hr ABPM	24-hour ambulatory blood pressure monitoring
aAOBP	attended Automated Office Blood Pressure
aABPM	attended Automated Blood Pressure Measurement
AESA	Alliance for Accelerating Excellence in Science in Africa
AOBP	Automated Office Blood Pressure
BP	Blood Pressure
CGMRC	Centre for Geographic Medical Research - Coast
CHWs	Community Health Workers
CHU	Community Health Unit
CLG	KWTRP Community Liaison Group
CVD	Cardiovascular Disease
ECG	Electrocardiogram
ESRC	Economic and Social Research Council
HBP	High Blood Pressure
HBPM	Home Blood Pressure Measurement
HMOD	Hypertension Mediated Organ Damage
KCS	Kenya Cardiac Society
KHDSS	Kilifi Health and Demographic Surveillance System
KWDSS	Kiang West Demographic Surveillance System
KWTRP	Kemri-Wellcome Trust Research Programme
LSHTM	London School of Hygiene and Tropical Medicine
MRC	Medical Research Council
MRCG	Medical Research Council Unit The Gambia
MS	Microsoft
NCD	Non-Communicable Diseases
NIHR	National Institute for Health and Care Research
ODK	Open Data Kit
PASCAR	Pan African Society of Cardiology
POC	Point of Care
SOP	Standard Operating Procedure
SSA	sub-Saharan Africa
TOD	Target organ damage
TTE	Transthoracic echocardiogram
uAOBP	unattended Automated Office Blood Pressure
uABPM	unattended Automated Blood Pressure Measurement
UON	The University of Nairobi
WHO	World Health Organisation

Abstract

Background:
Sub-Saharan Africa (SSA) has one of the highest estimated prevalence of hypertension worldwide. The impact of hypertension is of particular concern in rural SSA. One suggested approach to improve the management of people with high blood pressure in rural SSA is to use a community-centred approach, where care is more actively promoted and brought into the community to remove obstacles in accessing it. To develop a community-centred programme we need to identify optimal approaches to risk stratify patients with elevated blood pressure.

Methods:
We will conduct a cross sectional study in 1250 adult participants from Kilifi and The Gambia. The overall aim of the study is to improve the evidence base for diagnosis and risk estimation for a CHW-led community centred hypertension programme in two rural communities in SSA. We will do this through five objectives as follows: (1) determine the accuracy of three alternative blood measurement methods performed by community health workers in identifying people with hypertension (HTN) in rural SSA, compared to the reference standard method; (2) determine the relationship between systolic blood pressure with potential risk factors; (3) determine the prevalence of target organ damage (TOD) in a hypertensive population in rural SSA; (4) determine the accuracy of innovative point of care (POC) technologies to identify patients with TOD in rural SSA; and (5) determine the cost-effectiveness of different combinations of blood pressure and TOD measurements to initiate treatment in people with HTN in SSA.

The diagnostic accuracy of the blood pressure and point of care parameters will be estimated using diagnostic parameters (sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios) against the reference standard or conventional measurement method (as applicable). We will conduct risk factor analyses using multivariate linear and logistic regression methods; estimate prevalence rates of TOD including stratified and age and sex- standardised prevalence rates; and cost effectiveness modelling studies comparing the cost effectiveness of different decision-making approaches for initiating treatment.

Expected findings:
The results of this study should determine the accuracy of different types of BP measurement methods, the prevalence of TOD in rural SSA and the accuracy of innovative point of care technologies to identify patients with TOD. The comparative cost-effectiveness of different decision-making approaches for initiating treatment of hypertension will be modelled and finally used to develop a community-centred programme to improve care for hypertensive patients living in rural SSA.

1. Background

1.1. Burden of hypertension in rural sub-Saharan Africa

Hypertension is the single risk factor that accounts for the highest number of deaths (10.8 million) globally(1, 2). Sub-Saharan Africa (SSA) has one of the highest estimated prevalence of hypertension worldwide (Figure 1), and in 2019 hypertension was implicated in almost 700,000 deaths - double the number in 1990(1, 2). In SSA, hypertension occurs at younger ages, is more severe, remains very poorly controlled, and is more likely to cause complications including heart failure, stroke, kidney disease and premature death than in other regions(3, 4). The impact of hypertension is of particular concern in rural

SSA where 60% of the region's 1.1 billion population live. While hypertension prevalence appears to be as high in rural as in urban settings, hypertension awareness, treatment and control is lower (5-7).

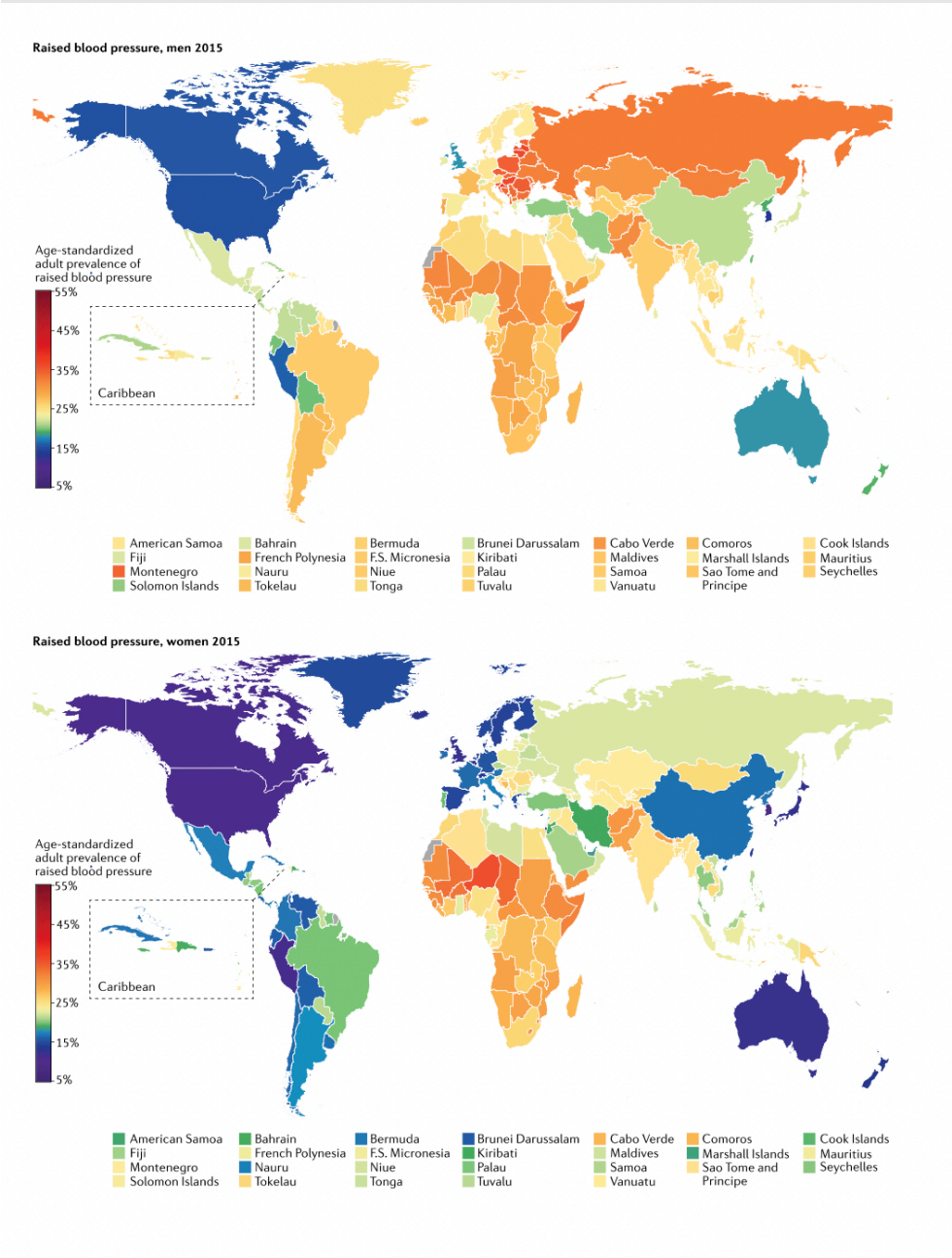

Figure 1: Cartogram showing prevalence of raised blood pressure by country in men (top panel) and women (bottom panel) (2)

1.2. Barriers to management and control of hypertension in SSA

To significantly reduce hypertension related burden, there is a need to improve the whole hypertension control cascade from awareness (through screening and diagnosis) to treatment (risk stratification and initiation of treatment) and control (monitoring, adherence and referral) (Figure 2)(8). The barriers to effective hypertension management in rural SSA are multiple and complex. They include *at the individual-*

level, the asymptomatic nature of hypertension, lack of understanding of its potentially serious consequences and competing priorities around home and work, which often mean that people only seek care very late when experiencing complications(9-13). These barriers are compounded by misconceptions about aetiology and potential benefits of pharmacotherapy(12). *At the provider-level,* barriers include poor communication between providers and with patients, lack of skills and competencies, poor infrastructure, and lack of adequate referral systems for care(14). *System-level* barriers include poor access to health care facilities, particularly in rural areas, with overcrowding at clinics and consequent long waiting times; limited, inconsistent or undersupply of antihypertensive medications; lack of affordability of treatment with poor coverage of national health insurance schemes; and underinvestment in health service capacity.

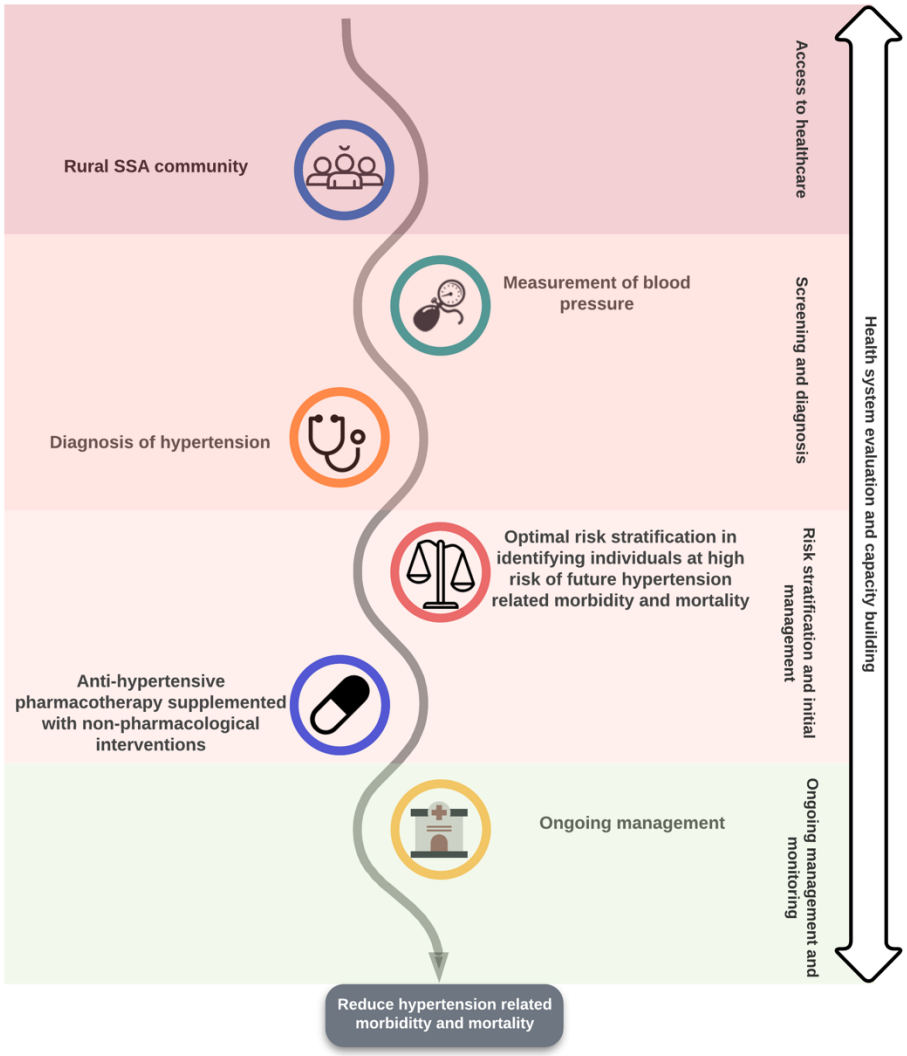

Figure 2: Schema summarising the hypertension control cascade to reduce the burden of hypertension related morbidity and mortality

1.3. Potential impact of a community-centred approach to manage people with hypertension

There is growing evidence from other regions where access to medical care is impeded by long distances to facilities (as in rural SSA) that community health workers (CHWs) can play a key role in managing hypertension and its consequences(15-17). For example, the HOPE-4 study, conducted in Colombia and Malaysia, showed that a community-centred multifaceted intervention including screening, diagnosis and treatment with combination pharmacotherapy administered by CHWs and supported by electronic

decision support tools improved blood pressure control(18). Similarly, the COBRA study, in Southeast Asia also showed improved hypertension management delivered using a community-centred intervention by CHWs(19). This evidence base has led organizations such as the Pan African Society of Cardiology (PASCAR) to advocate for community-centred approaches to improve hypertension management in SSA(20).

1.4. Limited evidence for implementing a community-centred approach to hypertension in rural SSA

Although the studies mentioned above are promising, no equivalent studies in SSA have been conducted. Moreover, the sustainability of the approaches trialled in these studies is of concern. A key unaddressed challenge is how to embed any new intervention approach within the local health system, especially when CHWs are given more responsibilities without a parallel increase in resources and clinical supervision. To be feasible and sustainable, a community-centred approach to managing hypertension must take account of the health system context, beyond simply the clinical protocols.

Aside from these structural challenges, there is limited evidence regarding some clinical recommendations in the rural SSA context. Specifically, it is unclear whether recommended approaches to the diagnosis of hypertension and estimation of cardiovascular risk are appropriate and effective for use in this setting. The decision to treat people with hypertension is based on diagnosis (through blood pressure measurement) and estimation of individual cardiovascular risk. Clinical guidelines, largely developed based on high-income country studies, ubiquitously incorporate these two aspects when recommending pharmacotherapy(21, 22). International guidelines recommend repeated Office/Clinic based Blood Pressure (BP) Measurement such as Automated Blood Pressure (ABP) measurement, which can be performed with (attended) or without (unattended) a health worker present, which can mitigate for white coat hypertension. Home Blood Pressure Measurement (HBPM; described below in Table 1) or 24-hour ambulatory blood pressure monitoring (24-hr ABPM) are also deemed to have a role. However, as we have previously reported these international recommendations for how to measure BP might not be accurate, feasible or cost-effective in SSA(23, 24). While it is accepted that people with a BP of >=160/100 mmHg should be prescribed anti-hypertensives, the International Society of Hypertension guidelines only recommend initial pharmacotherapy as essential for individuals with >140/90 mmHg when they are considered to be at high cardiovascular disease (CVD) risk(25). However, the validity of existing risk scores (recommended approach to estimate risk) in rural SSA is questionable. First, these risk scores were mainly developed in populations where the prevalence of other risks such as smoking and high cholesterol is much higher than in rural SSA(26-28). Second, compared to high-income countries, most studies in SSA show a substantial burden of hypertension on younger age groups. Current risk scores strongly weight age, invariably classifying these younger individuals at low risk. When we estimated CVD risk using the WHO Risk Score in Kenya and The Gambia (settings where our study will take place), none of those with >140/90 & <160/100 considered at high risk (>20% risk of cardiovascular events in the next 10 years) were younger than 60 years old (Figure 3). This is particularly pertinent given that age-adjusted cardiovascular event rates are higher in low- and middle-income countries than in high-income settings, and many people in SSA would have already suffered the clinical complications of hypertension by age 60 (we recently showed that average age at which women in Kenya suffer a stroke is 60 years)(29, 30). Finally, current risk scores do not consider region-specific factors in SSA, including co-existing chronic communicable disease such as HIV and malaria, or exposure to environmental factors (for example indoor air pollution)(31-33). In addition, genetic factors such as the high frequency of malaria and trypanosomiasis protective polymorphisms (for example Dantu, SCT, APOL1 or APOL2) could be contributing to the different epidemiological picture of hypertension and target organ damage (TOD) in SSA(34, 35).

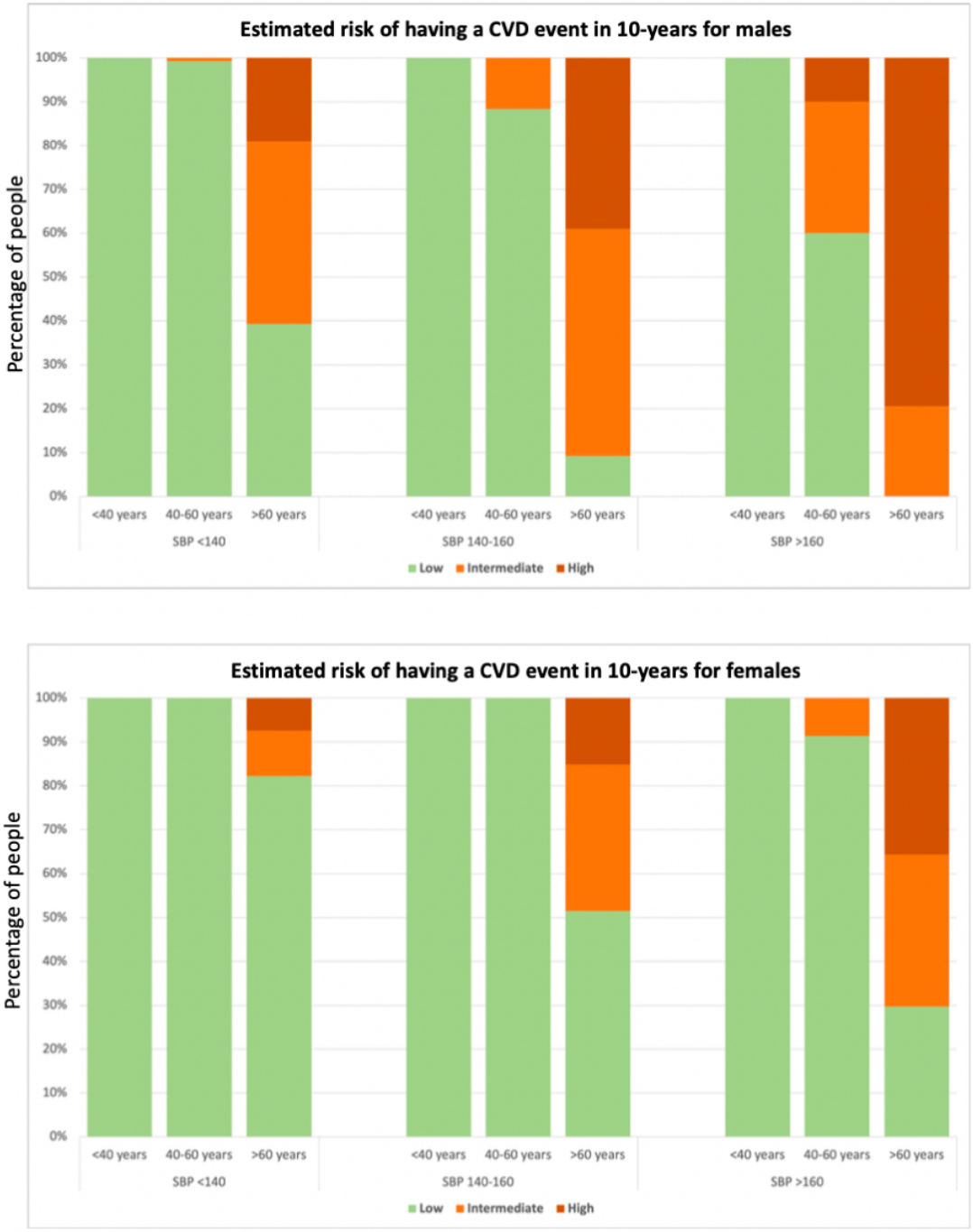

Figure 3: Stack plot showing proportion of the population estimated to be at low, intermediate and high cardiovascular risk by age and systolic blood pressure in males (top panel) and females (bottom panel) in Kenya (based on 4,338 participants from rural Kilifi). Low risk is defined as <10% chance of having a cardiovascular event within 10 years, medium risk is defined as a 10-20% chance and high risk is defined as >20% chance.

1.5. What we need to know to implement an effective and sustainable community-centred approach for people with hypertension in rural SSA

To improve hypertension management through a sustainable community-centred approach in rural SSA, we need to conduct research in two inter-related domains.

1) Identifying optimal approaches to diagnose and risk stratify patients with elevated blood pressure. Specifically, we need to better understand the validity and feasibility of the different diagnostic approaches when conducted by CHWs at the community level in SSA, and to find better approaches for risk stratification that will work in a CHW-led system. For the latter, given the absence of valid risk scores for SSA populations, we propose to measure target organ damage (TOD; i.e. subclinical changes of the brain, heart, eyes, or kidneys). We will measure TOD with standard reference tools and provide the first validation data for point of care measurement techniques in this setting.

2) It is also vital to systematically assess the health service and system structures into which the community-centred intervention will be introduced. We need to explore the patient, community, health care provider and decision-maker experiences and perspectives as well the broader regulatory, fiscal, economic, and policy environment to understand the key factors that are necessary for the successful implementation, sustaining, and potential scaling-up of the intervention.

This protocol covers the first domain. The second domain is covered by a separate protocol that describes a research programme that will run in parallel with the work described in this protocol. Both domains are part of the wider IHCoR-Africa project. The findings from both will contribute to a final piece of work that develop a new community-based intervention for improving hypertension management and test it in a cluster feasibility trial.

1.6. Justification

People living in rural sub-Saharan Africa have a very high prevalence of hypertension, but very few are controlled. Scalable methods to improve the detection of such individuals and to determine who among them requires treatment are urgently needed. In this study we aim to test innovative methods of detecting hypertension and target organ damage that can then be applied on a wider scale in similar resource limited settings.

2. Objectives

2.1. Overall Objective

In this study we will seek to improve the evidence base for diagnosis and risk estimation for a CHW-led community-centred hypertension programme in two rural communities in SSA.

2.2. Specific Objectives

Objective 1. To determine the accuracy of three alternative blood pressure measurement methods relative to the reference standard, all assessed by CHWs, to identify individuals with hypertension in rural SSA

Objective 2. To determine the relationship between systolic blood pressure with potential risk factors (e.g. body mass index and genotype)

Objective 3. To determine the prevalence of TOD in a hypertensive population in rural SSA

Objective 4. To determine the accuracy of innovative point of care technologies to identify patients with TOD in rural SSA

Objective 5. To determine the cost-effectiveness of different combinations of blood pressure and TOD measurements to initiate pharmacological treatment in people with hypertension in rural SSA

3. Study Design and Methodology

3.1. Study Setting

Activities will take place across two rural sites, one in East Africa (Kilifi, Kenya) and another in West Africa (Kiang West, The Gambia). Both settings have a high burden of hypertension, as well as a well-developed research infrastructure to facilitate our work.

Kilifi County in Kenya is one of the poorest regions in the country(36). The Kilifi Health and Demographic Surveillance System (KHDSS) where the study will be conducted, covers an area of 900 km^2 and has a population of around 300,000 people. The prevalence of hypertension is 26% and only 3% of individuals have their blood pressure controlled (37). Further evidence of the consequences of poor hypertension control is the high incidence of cardiovascular disease in the area, with more than one third of patients admitted with cardiovascular disease dying during their hospital stay (30). Community health workers deliver health services at the community level (first level of care). CHWs work within a Community Health Unit, which is a health service delivery structure within a defined geographical area covering approximately 5,000 people. CHWs are selected from the community they serve and where possible, required to have completed O-level education. Each CHU is required to have approximately 10 CHWs serving a population of 5000 people (500 – 1000 households).

The Kiang West district in The Gambia covers 750km^2 and comprises 36 villages with a population of over 14,000 individuals. It is one of the poorest regions in the country with all households in the lowest or low wealth groups. In our analysis of the 2010 WHO STEPS NCD data, we found a hypertension prevalence in this region of 40%, of whom 71% were previously undiagnosed, and only 4% were controlled. The health service delivery in the region is coordinated through the Regional Health Team of the Lower River Region (Mansakonko Administrative Area). The community health nurses (CHNs) deliver services in a defined cluster within a district. There are 4 CHNs in Kiang West with each handling a cluster of 7-9 villages, working with village health workers (VHW) whose activities they supervise. The VHWs are selected by their respective communities.

3.2. Study Population

We will select an age-stratified random sample of participants aged ≥30 years from the population registers of the Kiang West Demographic Surveillance System (KWDSS, The Gambia) and Kilifi Health and Demographic Surveillance System (KHDSS, Kenya)(38, 39). The following strata will be used: stratum 1: ≥30 - <40, stratum 2: ≥40 - <50, stratum 3: ≥50 - <60, stratum 4: ≥60 - <70 and stratum 5: ≥70. We will exclude pregnant women for two reasons. Firstly, due to technical difficulties in conducting some of the study measurements (for example, echocardiography). Secondly, our study is not looking at gestational hypertension which remains important but beyond the scope of our aims and objectives.

The participant recruitment approach is shown in Figure 6.

3.3. Inclusion and Exclusion Criteria

The eligibility criteria listed here reflect the population who will be invited to participate in Objectives 1, 3, and 4. Objectives 2 and 5 do not require specific study procedures, only data collection.

3.3.1. Inclusion criteria

- Registered in population registers of the Kiang West Demographic Surveillance System (KWDSS, The Gambia) or Kilifi Health and Demographic Surveillance System (KHDSS, Kenya)

- Aged ≥30 years at the time of enrolment in the study
- Able to provide written informed consent to participate in the study

3.3.2. Exclusion Criteria

- Participants not able to perform any one of the study procedures
- Pregnant women (self-reported)

3.4. Participant consent

Informed consent will be obtained from all participants in the study and the informed consent procedure will be conducted by trained community health workers. Full details of the informed consent procedure are given in section 10.

3.5. Sample Size Determination

3.5.1. Objective 1

Assuming a prevalence of hypertension detected by the reference standard method (24-hr-ABPM) of 25-35%, we will require 832-1003 participants in order to generate validity parameters for hypertension prevalence with a precision of ±3% overall and ±5% at each of the two sites (23, 37). We have made a provision for loss of data in 25% of participants due to poor data quality, taking the total number of participants required to 1250, equally divided between Kilifi and Kiang West.

3.5.2. Objective 2

Assuming for illustrative purposes, that 10% of individuals will be either obese or have any of the putative genetic markers, and that the standard deviation of systolic blood pressure will be 15 mmHg, then 1,003 participants will provide at least 80% statistical power for an alpha of 0.05 to detect a 4mm Hg difference in systolic BP in those with and without the exposure of interest.

3.5.3. Objective 3

Assuming a prevalence of hypertension detected by the reference standard method (24-hr-ABPM) of 30%, we estimate that approximately 300 participants from those recruited in Objective 1 will be classified as hypertensive. With 300 hypertensive patients, we would be able to estimate the confidence interval for a conservative TOD prevalence of 35% with lower and upper intervals of 29.7% and 40.4% respectively, and that we will have over 95% power for an alpha of 0·05 to test the null hypothesis that the prevalence of TOD is below 25%.

To further explore the difference in the prevalence of TOD in the hypertensive and general population, we intend to assess all participants recruited into Objective 1 for TOD.

3.5.4. Objective 4

When measured with the reference standard techniques, we expect a 35% prevalence of TOD among the 300 estimated hypertensive participants and approximately 5% prevalence in the remaining non-hypertensive participants. This will provide us with a total available sample of 153 participants with TOD. Assuming at least 85% sensitivity of detection of TOD by the point-of-care (POC) strategies we will have at least 80% power for an alpha of 0.05 to test the null hypothesis that the sensitivity is below 75%. While we project that 105 participants will have TOD from the measurements taken in Objective 3, we will conduct POC TOD assessments on all participants.

3.5.5. Objective 5

A sample size estimation is not appropriate for this objective as explained below.

The primary outcome measure for this objective is the incremental cost effectiveness ratio (ICER) for different methods of BP and TOD measurement to initiate pharmacological treatment of hypertension in rural Africa, and the confidence intervals around the differences in ICERs will be calculated using bootstrap methods. The computation of the ICERs will take in several inputs including data on validity of the various measurement methods as obtained in the preceding objectives and costs and effectiveness measures obtained from a combination of data collected within the IHCoR-Africa project and external data.

3.6. Sampling Procedures

To make sure to obtain a random and representative sample from the two study areas, a random sample will be selected from the total registered populations from the KWDSS, The Gambia and the KHDSS, Kenya. A random sample will be selected from both Demographic Surveillance Systems by simple random sampling. Half of the study population will be selected from the Gambian register and the other half from the Kenyan register. The following strata will be used: stratum 1: ≥30 - <40, stratum 2: ≥40 - <50, stratum 3: ≥50 - <60, stratum 4: ≥60 - <70 and stratum 5: ≥70.

3.7. Study procedures

3.7.1. Objective 1

We will conduct a cross-sectional study over two weeks to determine the accuracy of three alternative blood pressure measurement methods performed by CHWs in identifying individuals with hypertension in rural SSA relative to the reference standard. An overview of the four methods is given in Table 1. The CHWs will be trained at KWTRP by the study team to perform the blood pressure measurements based on study SOPs. The competencies of the CHWs will be assessed by the study team prior to data collection and at regular intervals during data collection. The CHWs will then collect blood pressure measurements in a random order at participants' homes. The random order of blood pressure measurements for each of the participants will be set using a computer-generated randomisation list produced prior to measurements starting.

Table 1: Overview of the methods used to measure blood pressure

Method	Abbreviation	Short description
Reference method (gold standard)		
24 Ambulatory BP Measurement	24-hr-ABPM	24-hr-ABPM measures blood pressure on a continuous basis for 24 hours at fixed time intervals. The device will be attached to the body and has to be carried around by the participant for one day.
Alternative methods		
Attended Automated Blood Pressure Measurement	aABPM	A CHW will conduct a blood pressure measurement using an automated machine and record the readings.
Unattended Automated Blood Pressure Measurement	uABPM	An automated blood pressure machine will be used to record a participant's blood pressure without having the CHW present in the room.
Home BP measurement	HBPM	The participant receives a digital blood pressure machine at home and is asked to record their blood pressure every morning and evening for 7 consecutive days.

aABPM and uABPM

Attended and unattended Automated Blood Pressure Measurements (aABPM and uABPM), which take 10-15 minutes to conduct, will be performed at the homes of study participants, but otherwise following international recommendations on how to perform the measurements (40, 41). Both the CHWs and the participants will be blinded to the results of the aABPM and uABPM as the devices will be programmed to not display the BP. Once the CHW has completed both sets of measurements, the CHW will then retrieve the results of the measurement from the device and enter them into the study case record form for onward relaying to the study database.

HBPM

HBPM will consist of morning and evening measurements performed by the individual participant themselves for 7 days in a row. Instructions for HBPM will be given to the participants by the CHWs. The device will automatically store HBPM readings, which will be downloaded onto a computer/tablet when the CHWs come to collect the device from the participant. We will also request literate participants to write down their daily HBPM measurements in diaries that we will supply to them.

24-hr-ABPM

The reference standard against which aABPM, uABPM and HBPM will be compared, will be the 24 ambulatory BP measurement (24-hr-ABPM). After attaching the 24-hr-ABPM devices to the participants and giving them a few instructions, the CHWs will leave and then return after 24 hours to collect the device and transfer data collected onto a tablet/computer.

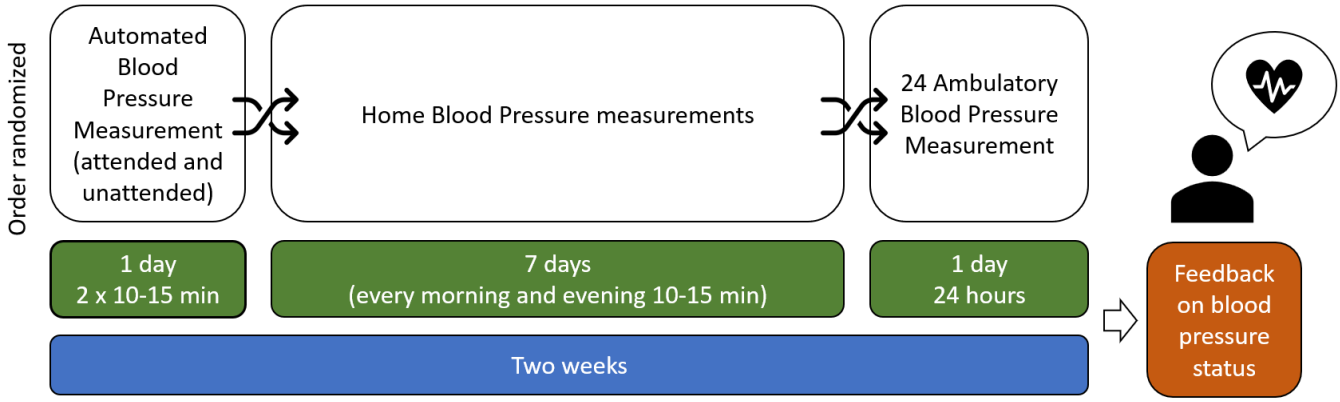

Figure 4:Schematic overview of blood pressure measurements performed in each participant

Each participant is expected to have completed all four BP measurements over a two-week period. A schematic overview of the procedure is shown in Figure 4. We will follow relevant international cardiological society guidelines for conducting all BP measurements (42-44).

Other variables collected

In addition to the blood pressure measurements, information will be collected on demographics, household assets, anthropometrics, diet, physical activity, history of hypertension and medication use (for hypertension and other diseases).

Feedback

We will ask the participants a few questions about their experience using the four blood pressure measurements after their final blood pressure measurement. The questions will cover their experiences regarding the acceptability, appropriateness and feasibility of use of the four blood pressure measurements at home.

BP results will be communicated to the participant after all four measurements have been performed. The meaning of the results will be explained and the participant gets the opportunity to ask questions about

the results. If the participant is hypertensive, they will receive advice on future care including referral to the appropriate local facilities for further management.
For participants with severely elevated blood pressure, referral to further care will be made at the time of measurement. If a participant has a blood pressure reading of ≥180/110 mmHg, they will receive immediate urgent referral to the best available local care. If a participant has a reading ≥160/100mmHg and <180/110mmHg, they will provided referral advice at the time of measurement so that they can seek treatment. This will be done for the 24-hr-ABPM and the aABPM and uABPM. For the HBPM, guidance will be given to participants about what to do, including contact details, if they receive BP measurements in excess of 160/100mmHG.

Variables to be collected

- Measures for BP from four BP measurements
- Awareness of BP status / hypertensive status
- Clinical history (e.g. tobacco consumption, alcohol consumption, diabetes, stroke, HIV, coronary heart disease, previous diagnosis hypertension, family history)
- Demographic variables (e.g. sex, age, household size)
- Anthropometrics (e.g. height, weight, body composition)
- Treatment BP (which medication is used and when)
- Household assets (standardized questionnaire)
- Dietary history (standardized questionnaire)
- Physical activity (hours a day active/exercising)

3.7.2. Objective 2

Objective 2 will make use of data and measurements gathered as part of Objectives 1. For the genetic analyses, DNA will be extracted from whole blood samples using Qiagen DNA Blood Mini kit. DNA extraction will make use of blood samples drawn for TOD measurement in Objective 3 and no new blood sample is required. We will then use PCR to determine presence of the genotypes of interest, as described in section 1.4. These analyses will be conducted in KWTRP.

3.7.3. Objective 3

We will conduct a cross-sectional study to assess the prevalence of TOD using reference-standard clinical assessments. The study measurements will be completed at a clinical visit. During this visit, aABPM and uABPM measurements will be repeated to assess the reliability of the home aABPM and uABPM measurements compared to those done at the hospital.

The clinical visit will use reference standard diagnostic tools to detect the presence of target organ damage to the heart, eyes or kidneys. These tools are shown Figure 5 and Table 2.

Type of target organ damage	**Reference-standard assessment technique**	**Point of care assessment technique**
Left ventricular hypertrophy	- *Transthoracic echocardiogram* - *12-lead ECG*	*Smartphone based 6-lead ECG*

Left ventricular systolic function	*Transthoracic echocardiogram*	*Smartphone based 6-lead ECG*
Retinopathy	*Clinical grade retinal cameras*	*Smartphone-based portable retinal camera*
Renal dysfunction	*Clinical laboratory assessment of whole blood and urine dipstick*	*Point-of-care clinical chemistry devices*
Arterial stiffness	*Tonometric measurement of pressure wave velocity*	*Blood pressure cuff-based measurement of pressure wave velocity*

Table 2: Summary of reference-standard and point of care assessments of TOD

3.7.4. Objective 4

We will conduct a cross-sectional study to validate the accuracy of point-of-care (POC) assessments of TOD compared to the reference-standard methods used in objective 3. For each type of TOD assessed, we will conduct additional point-of-care measurements at the same time as the reference-standard assessments are made as part of Objective 3. These assessments are shown in Figure 5 and Table 2.

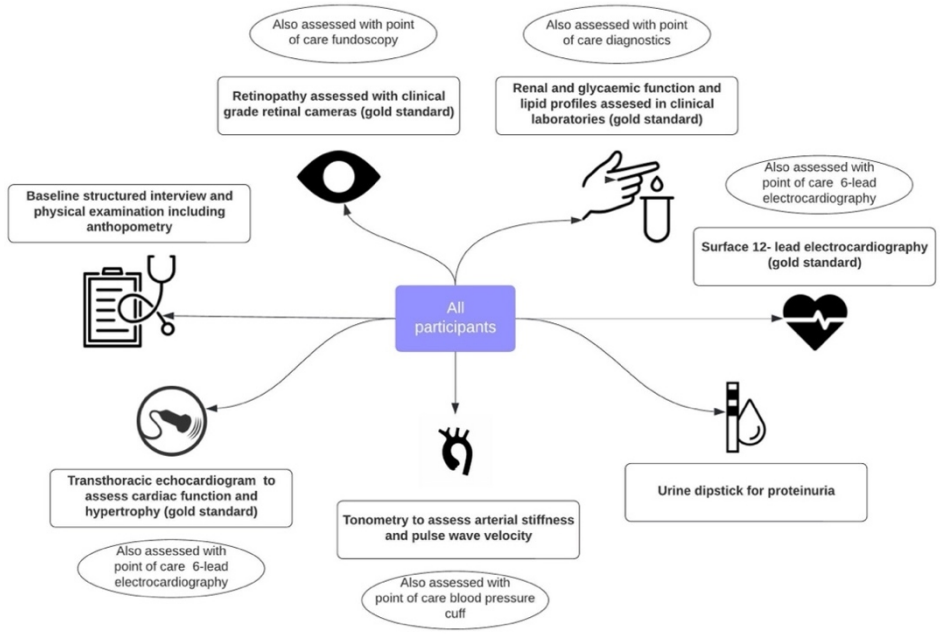

Figure 5: Schematic overview of measurements performed in each participant for Objectives 3 and 4

3.7.5. Objective 5

We will collect primary data on patient costs including the opportunity cost of time spent administering blood pressure-monitoring methods, missing productive activity and any out-of-pocket costs incurred for undergoing study procedures. Health system cost data will be collected using structured questionnaires to three CHWs from each study site and structured observations (of inputs and CHWs /user time spent

administering BP measurement), and a survey using a structured questionnaire to about 200 individuals diagnosed with hypertension as we have previously done (45).