

Protocol

Protocol for: Siedner MJ, Magula N, Mazibuko L, et al. Home-based care for hypertension in rural South Africa. *N Engl J Med* 2025;393:1304-14. DOI: 10.1056/NEJMoa2509958

This trial protocol has been provided by the authors to give readers additional information about the work.

Supplementary Appendix 2

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Statistical analysis plan. No changes were made to the statistical plan

Supplement to:

Home-based hypertension care in rural South Africa

Mark J. Siedner, Nombulelo Magula, Lusanda Mazibuko, Nsika Sithole, Alison Castle, Siyabonga Nxumalo, Thabang Manyapelo, Shafika Abrahams-Gessel, Dickman Gareta, Joanna Orne-Gliemann, Kathy Baisley, Max Bachmann, Thomas A. Gaziano

Supplement Version Date: 26 July 2025

Supplement 2 Table of Contents

Initial Trial Protocol	1 - 35
Final Trial Protocol	36 - 71
Summary of Research Protocol Changes	72
Statistical Analysis Plan	73 - 82

Initial Trial Protocol

IMPACT-BP: Implementation of a Combination Intervention for Sustainable Blood Pressure Control in Rural KwaZulu-Natal, South Africa

Version 1: November 1, 2021

Africa Health Research Institute
Brigham and Women's Hospital
Massachusetts General Hospital

ABBREVIATIONS

AHRI	Africa Health Research Institute
ART	Antiretroviral therapy
BP	Blood pressure
CHW	Community Health Worker
CDS	Clinical Decision Support
CFIR	Consolidated Framework for Implementation Research
CKD	Chronic Kidney Disease
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DBP	Diastolic blood pressure
DM	Diabetes Mellitus
DoH	Department of Health
GFR	Glomerular Filtration Rate
HBPM	Home-based Blood Pressure Management
HTN	Hypertension
ICERs	Incremental cost-effectiveness ratios
KZN	KwaZulu-Natal
MI	Myocardial infarction
NCD	Non-communicable disease
NHLBI	National Heart, Lung, and Blood Institute
PCCs	Primary care clinic(s)
PHC	Primary health center
POC	Point of care
SA	South Africa
SBP	Systolic blood pressure
SOC	Standard of care
SOP	Standard operating procedure
QALYs	Quality adjusted life years

Table of Contents

- I. INVESTIGATORS AND INSTITUTIONS7**
- II. STUDY FUNDING AND REGISTRATION.....8**
- III. PROJECT SUMMARY AND SPECIFIC AIMS9**
- IV. AIM 1: READINESS AND ACCEPTABILITY ASSESSMENT 11**
 - A. Methods 11
 - B. Study Outcomes 12
 - C. Eligibility Criteria Rationale 12
 - a. Key Informants..... 12
 - b. Health Workers 12
 - c. Patients/Eligible Study Participants 12
 - D. Recruitment 12
 - E. Enrollment..... 12
 - a. Inclusion Criteria for Key Informants 12
 - b. Inclusion Criteria for Health Care Workers 13
 - c. Inclusion Criteria for Participant Focus Groups 13
 - F. Sample Size..... 13
 - G. Informed Consent 13
 - H. Data Collection and Analysis 13
 - a. Data Collection 13
 - b. Data Analysis..... 14
 - I. Risks, Protection from Risks and Benefits to Study Participation in Aim 1 14
 - a. Risks and Protections 14
 - b. Benefits..... 14
- V. AIM 2: IMPLEMENTATION CLINICAL TRIAL..... 15**
 - A. Aim 2 Overview..... 15
 - Figure 1. Study Schemia 15
 - B. Eligible Study Population 16
 - C. Eligibility Criteria 16
 - a. Inclusion Criteria 16
 - b. Exclusion Criteria 16
 - D. Subject Recruitment 16

a.	Participant Identification.....	16
E.	Informed Consent	16
F.	Randomization.....	16
G.	Aim 2 Study Procedures	17
a.	Blood Pressure Monitoring Procedures by Study Arm	17
i.	SOC: Baseline Visit for Clinic-Based Standard of Care Participants (Figure 2) 17	
Figure 2.	Standard of Care Model.	17
ii.	Intervention 1: Community Health Worker Care Model (CHW) (Figure 3)	17
Figure 3.	Intervention 1: CHW Care Model.....	18
iii.	Intervention 2: Enhanced community health worker-based with mobile health blood pressure monitoring model (eCHW+) (Figure 4).....	18
Figure 4.	Intervention 2: eCHW+ Care Model.	19
b.	Study Visit Schedule.....	19
i.	Visit 1: Enrollment	19
ii.	Visit 2: 6-month BP Measurement Assessment and Medication Use	19
iii.	Visit 3: 12-month BP Measurement Assessment and Evaluation of BP Device Function	20
iv.	Missing and Late Appointments	20
Table 1.	Summary of Study Visit Procedures	20
H.	Data Systems and Management	20
a.	Data Systems	20
i.	REDCap Study Database	20
ii.	Hypertension Management Application	21
b.	Data Protection and Confidentiality	21
c.	Specimen Collection and Testing	21
d.	Data Monitoring and Quality Control.....	21
I.	Study Monitoring and Regulatory Oversight	21
a.	Staff Training	21
i.	Research Staff	21
ii.	Clinical Study Staff.....	22
b.	Regulatory Oversight and Safety Monitoring.....	22
i.	Safety Monitoring	22
ii.	Adverse and Unexpected Event Reporting	22
J.	Statistical Considerations and Analyses.....	23

a. Sample Size.....	23
Table 2. Differences in change from baseline that can be detected with 80% power .	23
Table 3. Hypertension visits and patients at clinics in the study catchment area (2020)	24
.....	24
K. Study Outcomes	24
a. Primary Outcome of Clinical Trial	24
b. Secondary Outcomes	24
c. Safety Measures.....	24
L. Aim 2 Analysis Plan	24
M. Risks, Protection from Risks and Benefits to Study Participation in Aim 2	25
a. Risks and Protections	25
b. Benefits.....	25
VI. AIM 3.....	27
A. Methods.....	27
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	27
b. (Aim 3b) Cost-effectiveness.....	27
B. Study Outcomes	28
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	28
b. (Aim 3b) Cost-effectiveness.....	28
Table 4. Summary of acceptability, fidelity, and sustainability outcome measures for Aim 3a.....	29
C. Data Sources.....	30
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	30
b. (Aim 3b) Cost-effectiveness.....	30
D. Recruitment	30
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	30
b. (Aim 3b) Cost-effectiveness.....	30
E. Enrollment.....	30
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	30
i. Inclusion Criteria for Key Informants	30
ii. Inclusion Criteria for Health Care Workers.....	30
iii. Inclusion Criteria for Participants.....	30
b. (Aim 3b) Cost-effectiveness.....	31
F. Sample Size.....	31
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	31

b. (Aim 3b) Cost-effectiveness.....	31
G. Informed Consent	31
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	31
b. (Aim 3b) Cost-effectiveness.....	31
H. Data Collection	31
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	31
b. (Aim 3b) Cost-effectiveness.....	31
I. Analysis.....	32
a. (Aim 3a) Fidelity, Sustainability, and Acceptability	32
b. (3b) Cost and Cost-effectiveness	32
J. Risks, Protection from Risks and Benefits to Study Participation in Aim 3a and 3b.	33
a. Risks and Protections	33
b. Benefits.....	33
VII. REFERENCES.....	34

I. INVESTIGATORS AND INSTITUTIONS

Thomas A. Gaziano, MD MSc
Harvard Medical School
Tel: +1-617-432-4348

Co-Principal Investigator
Massachusetts General Brigham
Email: tgaziano@bwh.harvard.edu

Mark J. Siedner, MD MPH
Harvard Medical School
Tel: +1-617-726-4686

Co-Principal Investigator
Massachusetts General Brigham
Email: msiedner@mgh.harvard.edu

Max Bachmann, MD PhD MSc
Norwich Medical School
Tel: +44 (0)1603-59 1220

Co-Investigator
University of East Anglia
Email: M.Bachmann@uea.ac.uk

**Nombulelo Magula,
MBChB, MSc, FCP(SA), PhD**
Nelson R Mandela School of Medicine
Tel: +27 31 260 4238

Co-Investigator
University of KwaZulu-Natal
Email: magulan@ukzn.ac.za

Joanna Orne-Gliemann, PhD MPH
Bordeaux University
Tel: +33 (0) 5.57.57.45.17

Co-Investigator
Email: Joanna.Orne-Gliemann@u-bordeaux.fr

II. STUDY FUNDING AND REGISTRATION

Sponsor: National Heart, Lung, and Blood Institute (NHLBI)

Grant Number: NIH R01 HL144848

FAIN: R01HL144848

Study Period: September 04, 2020 – August 31, 2025

ClinicalTrials.gov registration Number: TBD

III. PROJECT SUMMARY AND SPECIFIC AIMS

Uncontrolled hypertension is the primary risk factor for stroke and hypertensive heart disease, which are the leading causes of non-communicable disease (NCD) deaths in South Africa, and of disability adjusted-life years lost globally [1-3]. Yet, there is a large knowledge-implementation gap between efficacy literature on hypertension control and effectiveness of health systems to provide hypertension care [4]. This is particularly true in resource-limited settings. In rural KwaZulu-Natal (KZN), we recently found that approximately one in six adults over 18 years old have hypertension, and fewer than one in four of those with hypertension have disease control [5].

The South African (SA) Department of Health (DoH) in its “Strategic Framework 2019-2024” has set a goal to increase life-expectancy through universal health coverage [6]. KZN Health has outlined its strategic goals to be consistent with the National goals to reduce morbidity and mortality through increased screening, treatment, and control of NCDs [7]. These goals will be achieved through an enhanced community-based care program, that will further integrate community health workers (CHWs) into the public health system, strengthen clinics, and implement a digital health strategy. The basic structure of the community-based program is the linkage of Ward Based Primary Care Outreach teams that are linked to the primary health center (PHC) facility and consists of a team of CHWs lead by an outreach team leader who is a trained nurse. The COVID-19 pandemic has accelerated the need for these changes which would allow community members to receive a greater portion of their care in their homes limiting overcrowding of clinics and decreasing infection risk.

The scientific goals of this project are to inform best practices for implementation of interventions targeting health systems and individual barriers to effective hypertension care in rural KwaZulu-Natal. We have selected a combination of interventions, effective in clinical trials but without widespread successful health system translation in resource-limited settings, that target both the health system and the individual to attain improved blood pressure control. Our intervention design specifically reflects support for community-based delivery of care for chronic diseases, that has been established to be effective in HIV care [8], increasingly prioritized in light of the COVID-19 pandemic [9] and is promoted by the South Africa Department of Health Non-Communicable Disease Control Program Policy Statements [10]. We will conduct a randomized trial to evaluate community-based hypertension control programs based on three primary components: a) community-based disease management with home-blood pressure measurements; b) a nurse champion for program oversight, and c) use of a clinical decision support system.

We will evaluate the implementation of two community-based, technology-supported programs to improve blood pressure control in South Africa, guided by the Conceptual Model for Implementation Research [11], with a focus on acceptability (Aim 1), effectiveness (Aim 2) and feasibility, cost- effectiveness and sustainability (Aim 3). We will leverage a 20-year partnership with the Department of Health, a multidisciplinary team of experts, and a recent health screening of approximately 18,000 individuals in the catchment area [5] to accomplish the above goals, and to accomplish the following aims:

Aim 1: Evaluate the acceptability and conduct a readiness assessment for implementation, of community-based hypertension, technology-supported interventions to reduce blood pressure in rural.

Guided by the Conceptual Model for Implementation Research, we will use mixed methods to assess organizational, healthcare worker, and participant readiness for implementation of the interventions. We will use results of the readiness assessments to refine final implementation strategies for the intervention.

Aim 2: Determine the effectiveness of a community-based, technology-supported intervention to reduce systolic blood pressure and increase blood pressure control among individuals with uncontrolled hypertension in rural South Africa. We will conduct a trial using CHWs in conjunction with in-home BP monitoring among approximately adults randomized to one of three different arms of hypertension care: 1) clinic-based standard of care model (SOC); 2) community health worker-based blood pressure monitoring model (CHW); 3) and enhanced community health worker-based model, including mobile health blood pressure monitoring model (eCHW+).

Aim 3: Determine the fidelity, sustainability, acceptability, and cost-effectiveness of community-based, technology-supported hypertension interventions to reduce blood pressure in rural KwaZulu-Natal.

The use of the CMIR (Aim 1) will be extended to evaluate the fidelity and sustainability of the intervention. A microsimulation model (CVD PREDICT) that uses individual-level risk factor data and health cost inputs will be used to determine the cost-effectiveness of the intervention.

IV. AIM 1: READINESS AND ACCEPTABILITY ASSESSMENT

Evaluate the acceptability and conduct a readiness assessment for implementation, of community-based hypertension, technology-supported interventions to reduce blood pressure in rural KwaZulu-Natal.

A. Methods

Guided by the Conceptual Model for Implementation Research [11] and the Theoretical Framework for Acceptability [12], we will use qualitative methods to assess organizational, healthcare worker, and patient acceptability of and readiness for the implementation of the intervention.

To do so, we will first host a series of key informant interviews and meetings, with representatives from the national DoH and other key stakeholders, which will allow us to assess pre-intervention implementation acceptability and readiness at the organizational level. These interviews/meetings will be designed to assess how the intervention aligns with health policy goals, current practice guidelines and services for hypertension, and institutional resources available to support the project.

Then group discussions will allow us to assess patient, nurse, CHW, and nurse supervisor perceptions about, and acceptability of, the intervention. We will explore areas such as workers' attitudes and beliefs about providing effective care to their patients (including self-efficacy), understanding of the intervention and expected effectiveness, relationships between workers and the primary care system (including perceived burden); we will also investigate patient perceptions of and need for hypertension care provided at the clinics.

These meetings and group discussions will be conducted approximately three months prior to study implementation. This approach allows for in-depth assessment of the initial acceptability of the intervention and to identify potential barriers and facilitators to the intervention and its implementation.

We will conduct selective (purposive) sampling of potential participants at the trial clinics, divided evenly between those who have controlled blood pressure and those who have uncontrolled blood pressure, and include both sexes and a range of ages for maximum variation. Health care workers will be selected from clinics that are included in the study. Participation in the health care worker groups will be determined by role, to encourage participants to share their opinions freely, given the strong hierarchical structure in clinical practice settings.

A major theme of the interviews will be readiness of the system infrastructure to support the intervention will also be assessed through an assessment of the capacity to support the interventions, including available cell phone coverage in the study area, data transfer capacity and processes, and piloting of the blood pressure monitoring app component of the intervention with nurses.

Added support for this intervention will be negotiated with community leadership structures such as the traditional leadership or Ward Councillor. Public health interventions have been

shown to have more positive health and psychosocial outcomes when there is community engagement [13]. This community engagement process will be incorporated into the Conceptual Model for Implementation Research and the Theoretical Framework for Acceptability.

These data will lead to a review the design of the intervention, if relevant, to refine its implementation through adaptations in the randomized clinical trial (Aim 2).

B. Study Outcomes

- Intervention acceptability, readiness, potential barriers and facilitators
- Potential intervention design modifications

C. Eligibility Criteria Rationale

- a. Key Informants: partners at the KZN DoH who are familiar with provincial and national health care policies, goals, and systems. These partners will provide important feedback on the alignment and fit of the proposed intervention with the current health priorities, goals, and availability of resources for hypertension care. Community leadership will also be interviewed as key informants in order to assess how the proposed intervention can be supported in community structures.
- b. Health Workers: clinic-based professional nurses, operational managers, outreach team leaders, physicians, CHWs, and pharmacists employed at clinics included in the trial. Each of these workers will provide rich data about their experiences providing specific components of clinical care to participants with hypertension, which will help with refining the implementation strategies, including adaptations, for the intervention.
- c. Patients/Eligible Study Participants: are expected to be receiving care for hypertension at the clinics included in the trial. Their experiences will be used to identify needs, potential barriers and facilitators to the intervention implementation, which will be considered when designing the implementation strategies of the study.

D. Recruitment

Key informants will be identified and contacted by study investigators at Africa Health Research Institute (AHRI) from current and prior collaborators working on improving health care in this rural population. Health care workers will be identified from personnel records at the study clinics and be invited to participate in the group discussions by study investigators, in agreement with DoH and AHRI policy for conducting research among health care professionals. Participants for group discussions will be identified from clinic registers for hypertensive patients.

E. Enrollment

- a. Inclusion Criteria for Key Informants
 - age 18 and over.
 - representative of the KZN DoH for involved in management of primary care delivery programs.
 - Ward Councillor or traditional leadership (Induna) in the community.

b. Inclusion Criteria for Health Care Workers

- age 18 and over.
- currently functioning as a health care worker (physician, nurse, CHW, pharmacist, clinic administrator/operational manager) at one of the study clinics.

c. Inclusion Criteria for Participant Focus Groups

- age 18 and over.
- diagnosed with both controlled and uncontrolled hypertension.

F. Sample Size

Final sample sizes for each of the participant groups will be driven by saturation of themes and in the following ranges:

- Key informants interviews/meetings: 8-10
- Group discussions with health care workers: approximately 2 or until saturation achieved
(number of participants per group: 8-10)
- Group discussions with patients/eligible future participants: approximately 2 or until saturation achieved
(number of participants per group: 8-10)

G. Informed Consent

Key informants will be invited to participate in interviews/meetings to discuss about the planned study and their participation will be taken as consent to participate. Study research assistants will recruit participants enrolled in the study and health care workers to participate in the group discussions. The research assistants will explain the activities of the study, how confidentiality will be maintained, and explain the informed consent form, as well as answer any questions. Those who agree to participate will be asked to sign two copies of an informed consent form. One copy will be given to the participant for his/her records and the other will be retained as part of the study record. For those who cannot sign their name, a thumb print will be obtained. If remote participation in group discussions are necessary due to the COVID-19 pandemic restrictions on in-person activities, verbal consent will be obtained and recorded prior to the start of the discussion.

H. Data Collection and Analysis

a. Data Collection

Names of key informants and data from key informants' interviews meetings will be kept confidential and will not be recorded. No personally identifiable data from these meetings will be used in publication or dissemination activities in any form. Data from both study participants and health care workers will be collected from group discussions. A Zulu-speaking research assistant with training in qualitative methods will facilitate the group discussions, which will be held in a private setting to ensure confidentiality and encourage maximum participation. The discussions will be recorded using digital audio. Health care workers and study participants will be asked to complete a short 5-10 item questionnaire and a generic study identification number will be assigned to each person completing the survey. Interviewers and focus group facilitators will use guides with open-ended questions to collect data. Discussions will cover pre-designated core topics such as understanding, perceptions and attitudes towards the planned intervention, any anticipated barriers, and opportunities for implementation.

b. Data Analysis

Group recordings will be transcribed and translated into English. Manual thematic analysis will be performed using a combination of theory-led (deductive) and data-led (inductive) coding. The study team will collaboratively review the data in both isiZulu and English to identify emerging codes and capture the richness of the data. Research assistants will conduct the primary coding of interview data. Their work will be supervised by at least 2 senior researchers who will perform double coding and review a subset of the research assistants' work to ensure uniformity and quality of the coding process. The senior researchers will review all the coded data and will create thematic summaries. Data management software package (NVivo) will be used to code and explore themes. Data on the acceptability of the intervention will be organized into the seven component constructs of the Theoretical Framework of Acceptability [12], which includes affective attitude, burden, ethicality, intervention coherence, opportunity costs, and perceived effectiveness.

Findings will contribute to identify key areas of the intervention implementation that will need specific attention for effective implementation. These results will be shared with the study team to identify processes in the randomized clinical trial protocol that may need to be adapted prior to implementation. Final training materials for health care workers participating in the trial will be updated to reflect these refinements in implementation.

I. Risks, Protection from Risks and Benefits to Study Participation in Aim 1

a. Risks and Protections

- i. The primary risk to participation is breach of confidentiality. We will not record names of any individuals taking part in interviews, nor will we report them in findings to be disseminated as part of this project. Given the low number of people in the study and the identification of participants (e.g., stakeholders in the Department of Health) it is possible that their identities could be inferred and we will make this risk clear during the consenting process.
- ii. A secondary risk of participation in this Aim is loss of time from participation in interviews and/or discomfort with the questions asked or nature of the conversations. All participation will be voluntary and participants will be free to pause, interrupt, or not respond to any questions or content areas that make them uncomfortable.

b. Benefits

- i. Most study participants in Aim 1 will derive no direct benefit from participation in the study.
- ii. Some participants might gain a personal sense of pride from knowing they are contributing to development of a system that intends to improve hypertension care in their community, or for the opportunity to contribute to its design.
- iii. If one of the interventions is ultimately successful, this study might provide a benefit to the community by helping to guide development of an improvement system of hypertension care.
- iv. A financial incentive of R50 of airtime (telephonic), R50 in cash (in-person), or a R50 food voucher will be provided to participants for their participation in discussion groups and interviews, subject to COVID-19 restrictions in place.

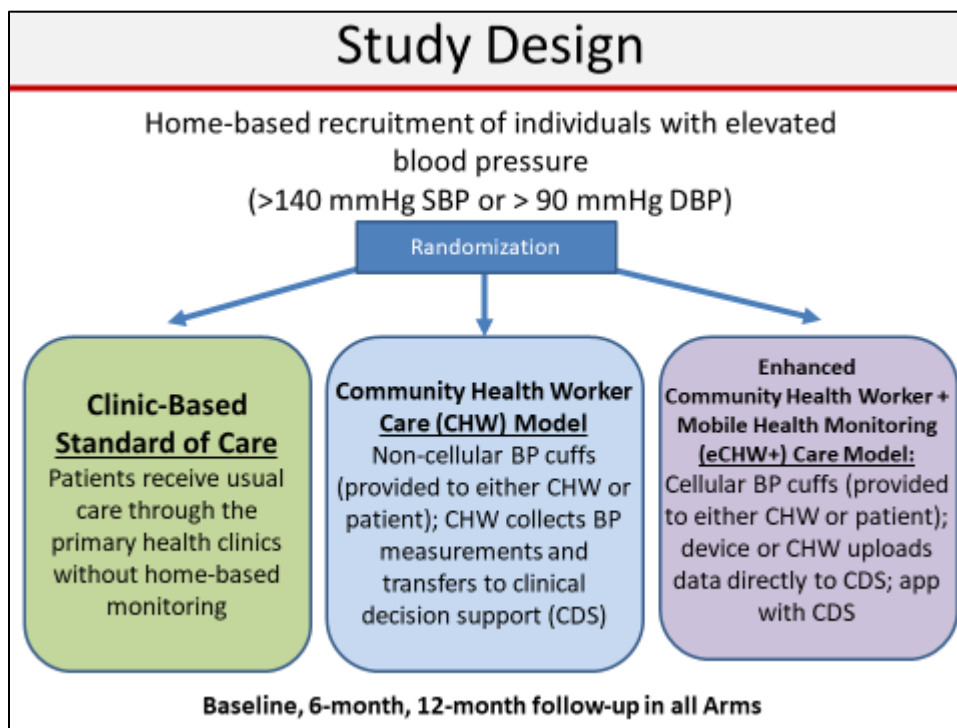
V. AIM 2: IMPLEMENTATION CLINICAL TRIAL

Determine the effectiveness of community-based, technology-supported interventions to reduce systolic blood pressure and increase blood pressure control among individuals with uncontrolled hypertension in rural South Africa.

A. Aim 2 Overview

This is randomized clinical trial intended to identify the optimal strategy of blood pressure management in rural South Africa. Participants will be randomized into one of three arms of hypertension care: 1) clinic-based standard of care model (SOC); 2) community health worker-based blood pressure monitoring model (CHW); 3) and enhanced community health worker-based with mobile health blood pressure monitoring model (eCHW+) (**Figure 1**). Eligible participants will be recruited from prior community-based hypertension screening programs, CHW-led hypertension screening activities, and/or from trial clinics where they are accessing care. Consenting participants will be randomized to one of the three study arms. Independent of clinical care, all participants will be seen at enrollment, at 6 months, and at 12 months for BP monitoring and data collection by study nurses for outcome assessments.

Figure 1. Study Schema



The primary effectiveness outcome will be assessed in an intention-to-treat analysis and defined as the change in systolic blood pressure (SBP) 6 months after enrollment. The secondary effectiveness outcome will be the proportion of participants with controlled blood pressure, as defined by an SBP <140 mmHg and a diastolic BP (DBP) <90 mmHg 6 months after enrollment.

B. Eligible Study Population

Residents living in the catchment area of publicly operated rural primary care clinics in the Umkhanyakude District in northern KwaZulu Natal.

C. Eligibility Criteria

a. Inclusion Criteria

- Age greater than 18 years old.
- Residing in uMkhanyakude District in northern KwaZulu-Natal.
- Elevated blood pressure (blood pressure > 140/90 mmHg) on two measurements.

b. Exclusion Criteria

- Pregnant or breast-feeding women.
- Severe, symptomatic hypertension with a measured blood pressure > 180/110 mmHg.
- Known, advanced chronic kidney disease. GFR < 60 ml/min/1.73 m².
- Currently use of at least 3 different anti-hypertensive therapies at full dose.
- Planning to move within the next 24 months.

D. Subject Recruitment

a. Participant Identification

We will identify potentially eligible participant from three sources: 1) those presenting to the trial clinics with elevated blood pressure, 2) individuals who are diagnosed with hypertension during home visits by CHWs, or 3) individuals with elevated blood pressure identifying through screening activities for hypertension conducted in the study catchment area, such as the Vukuzazi Study. Clinic and research staff from these activities will notify study nurses of potentially eligible participants who will then conduct eligibility assessments, either at the clinic, or in the case of notification after a home or community-based screening, at participant homes. Study nurses will confirm eligibility using a screening question, repeat blood pressure measurements, and conduct a point-of-care creatinine test (Abbott/Piccolo Xpress). Those who do not meet criteria but are confirmed to have uncontrolled hypertension or abnormal renal function will be referred to clinic for additional care.

E. Informed Consent

Informed consent procedures will be performed by research nurses who have been trained in the ethical conduct of human subjects research and informed consent procedures. This procedure will be carried out in the participant's home in either English or in Zulu.

F. Randomization

Consenting participants will be randomized by the REDCap randomization module to the standard of care (SOC), (CHW) or (eCHW+) study arms (**Figure 1**). Randomization will be stratified by clinic, active use of anti-hypertensive therapy, and ownership of a cellular phone. In brief, after screening has been completed, eligibility confirmed, and informed consent forms signed, a study participant is given a unique consecutive identification number in REDCap. The randomization field is selected, and the research assistant is informed which arm the participant has been selected for by the application. Strategy allocation will be unblinded to participants or clinic staff.

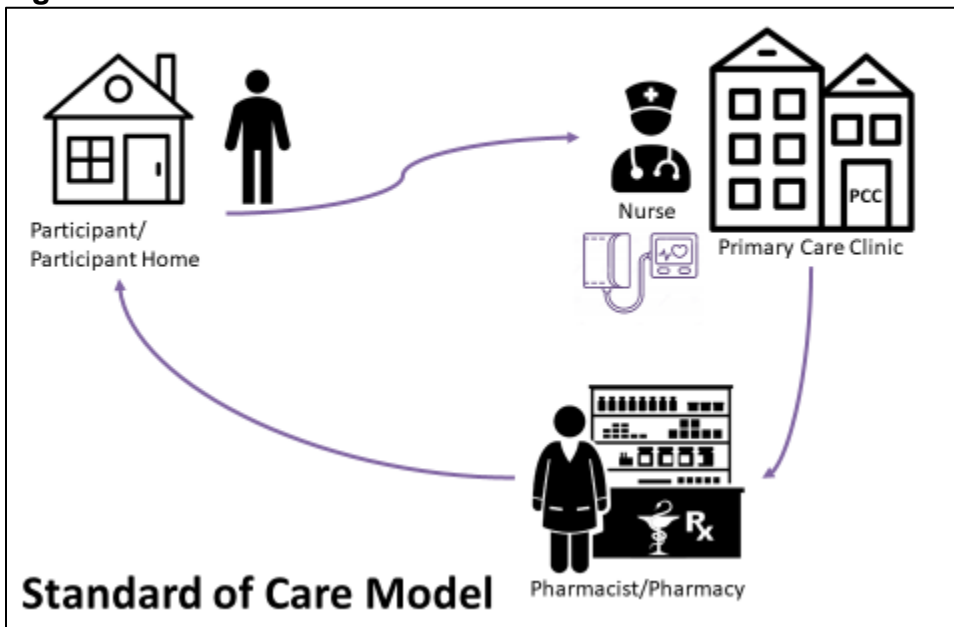
G. Aim 2 Study Procedures

a. Blood Pressure Monitoring Procedures by Study Arm

i. **SOC: Baseline Visit for Clinic-Based Standard of Care Participants (Figure 2)**

All study participants, including in the SOC arm, will receive standardized educational materials for BP medication adherence support, nutritional guidelines, and lifestyle medications for individuals with elevated blood pressure. Participants in the SOC arm will be referred to their clinic for initiation (if newly diagnosed) or active care (if previously diagnosed) as per standard clinical protocols. All care will be provided at the clinic. Routine care consists of recommended monthly visits to the clinic until BP is under control (<140/90 mmHg) and then at 6 monthly intervals. BP measurements to guide management decisions will be made at the clinic using standard clinic equipment. Symptoms related to hypertension and/or medications will be assessed at each visit. Medications available will include medications on the South African Essential Drug list and which are available in the pharmacy (which include hydrochlorothiazide, enalapril, amlodipine and atenolol). Prescriptions are picked up at the clinic pharmacy on a monthly basis. CHWs may also conduct monitoring as guided by clinical guidelines and as advised by their clinical supervisors during the study period to assess for adherence and provide education.

Figure 2. Standard of Care Model.

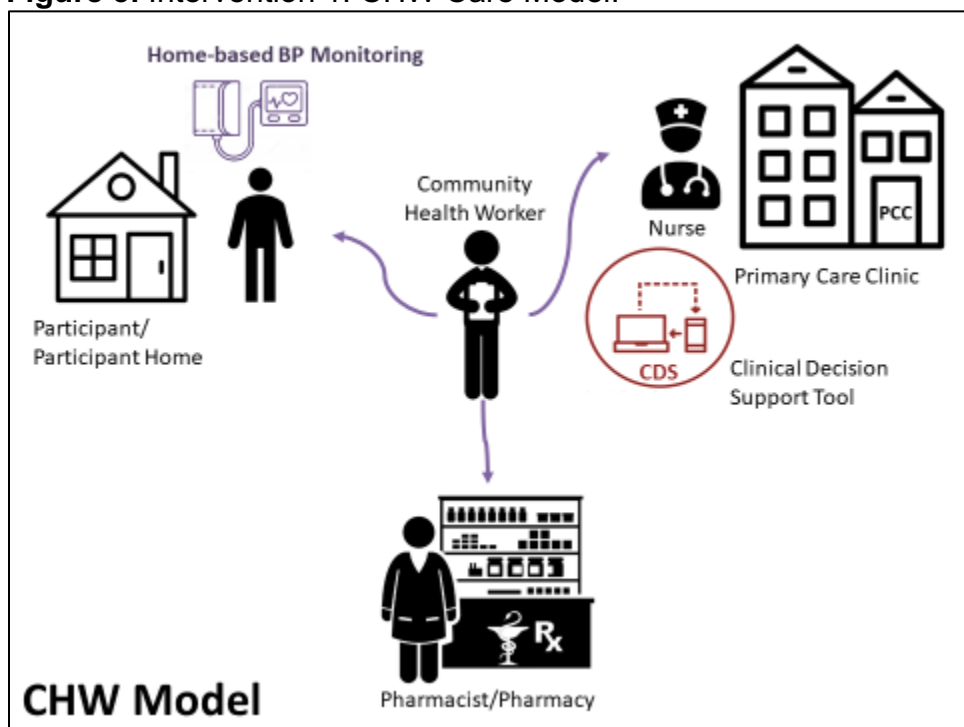


ii. **Intervention 1: Community Health Worker Care Model (CHW) (Figure 3)**

Participants in the (CHW) arm will be given an Omron BP Cuff and a standardized training on its operation, and assigned a CHW from their local Ward Based Primary Health Care Outreach Teams. Each team has Ward Based Leader who is a qualified nurse and is linked to the Primary Health Care facility. The participant will be instructed to take 6-10 measurements BP per week and record them in a logbook. CHWs will return to participant homes every 2-4 weeks to collect BP measurements and enter them into a data collection system, assess for symptoms, and discuss treatment adherence and lifestyle

recommendations. BP readings will be brought by the CHW to their assigned nursing supervisors, who will initiate and tailor medications based on a standardized clinical decision support algorithm, based on SA DoH hypertension control guidelines. All treatment decisions will be made by the nursing supervisors. Participants will either obtain medication(s) at the pharmacy or, as possible, have them delivered by a CHW. As per the SOC arm, medications used will include those on the South African Essential Drug list and which are available in the clinic pharmacy (include hydrochlorothiazide, enalapril, amlodipine and atenolol). Once a patient shows compliance and/or control prescription length can be increased from 30 days to 90 days. CHW visits will be spaced to once every three months as determined by the nursing supervisor, once blood pressure control has been achieved and sustained.

Figure 3. Intervention 1: CHW Care Model.

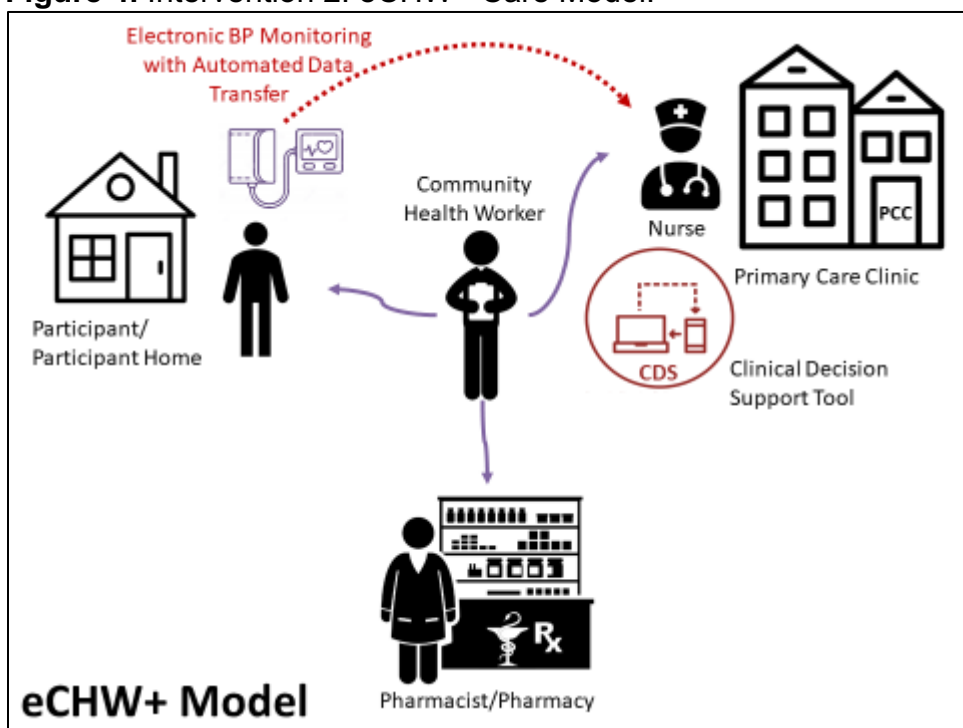


iii. Intervention 2: Enhanced community health worker-based with mobile health blood pressure monitoring model (eCHW+) (Figure 4)

Participants in the (eCHW+) Arm will also be given a BP Cuff, (but with cellular network capability, such that BP data can be directly transmitted to trial server), given training on its operation, and assigned a CHW from their local Community Health Team as in the CHW intervention 1 above. The participant will be instructed to take 6-10 measurements BP per week, which will be automatically uploaded onto the server to be made available by the nurse supervisors. CHWs will return to participant homes every 2-4 weeks to ensure functionality of the devices and transmission, collect BP measurements if the system is not functional, assess for symptoms, and discuss treatment adherence and lifestyle recommendations. Nursing supervisors at the clinic will use the remotely collected BP data to initiate and tailor medications based on the same standardized clinical decision support (CDS) algorithm, based on SA DoH hypertension control guidelines. All treatment

decisions will be made by the nursing supervisors. Participants will either obtain medication(s) at the pharmacy or, as possible, have them delivered by a CHW. As per the SOC arm, medications used will include those on the South African Essential Drug list and which are available in the clinic pharmacy (include hydrochlorothiazide, enalapril, amlodipine and atenolol). Once a patient shows compliance and/or control prescription length can be increased from 30 days to 90 days. CHW visits will be spaced to once every three months as determined by the nursing supervisor, once blood pressure control has been achieved and sustained.

Figure 4. Intervention 2: eCHW+ Care Model.



b. Study Visit Schedule

i. **Visit 1: Enrollment**

At Study Visit 1, participants will complete the baseline questionnaire to collect sociodemographic, clinical and treatment history, self-reported medication adherence, quality of life, and resource allocation data (**Table 1**). Enrollment BP measurements will be collected by study nurses (independently from the CHW program) using standard BP measuring devices (OMRON model). Three measurements will be taken from the seated position with five minutes between each measure [14]. As described during the recruitment phase, all participants will receive a point of care (POC) creatinine (Abbott/Piccolo Xpress) to determine both eligibility and to guide BP regimen selection. Study staff will also review participant clinic records (for those previously in care) to collect data on clinic treatment history and blood pressure measurements in the past.

ii. **Visit 2: 6-month BP Measurement Assessment and Medication Use**

A follow-up visit will be conducted by study staff will be performed for participants of all three arms approximately 6 months after enrollment (allowing for a one-month window).

BP measurements will be conducted by study nurses (independently from the CHW program) using standardized Omron BP cuffs. Three measurements will be taken from the seated position with five minutes between each measure [14]. At the 6-month visit we will additional collected data on medication regimen changes and adherence (**Table 1**).

iii. **Visit 3: 12-month BP Measurement Assessment and Evaluation of BP Device Function**

A final home-based study visit in all three arms will be conducted 12 months after enrollment (allowing for a one-month window period). BP measurements will be conducted using standardized Omron BP cuffs by study staff, independently of CHW interactions with study participants. Three measurements will be taken from the seated position with five minutes between each measure [14]. We will also collect data on self-reported medication regimen changes, adherence, quality of life, and resource use (**Table 1**).

iv. **Missing and Late Appointments**

If study participants are not present for study visits, study staff will attempt to call them to encourage another time for study visit. For participants who do not return calls within 7 days of a scheduled visit and unreachable, a study staff member will attempt to track them using a standardized lost-to-follow-up form and procedures. If participants are located, study staff will encourage them to allow for a follow-up home visit to complete procedures if the participant agrees.

Table 1. Summary of Study Visit Procedures

	Enrollment Visit	6-Month Visit	12-month Visit
Screening and eligibility form	<input type="checkbox"/>		
Consent form	<input type="checkbox"/>		
Point of care creatinine	<input type="checkbox"/>		
Sociodemographic questionnaire	<input type="checkbox"/>		
Tracking form	<input type="checkbox"/>		
Hypertension KAP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Medication adherence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hypertension treatment history	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Resource use form	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health related quality of life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blood pressure measurements	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chart review for medication and laboratory history	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

H. Data Systems and Management

a. Data Systems

i. REDCap Study Database

Study data will be directly entered into the study [REDCap Database](#). REDCap is a password protected, online database application that allows for storage of study data on encrypted servers in the United States. The application includes features for field limits, data quality control, study scheduling, randomization, and real-time study monitoring. Questionnaires and clinical records will be completed in real-time and entered by study staff using encrypted study mobile tablets. The REDCap application allows for both online

(real-time) data entry or, when internet service is not available, offline entry with syncing to the server when internet becomes available again.

ii. **Hypertension Management Application**

In both intervention arms, we will use a clinical decision support system (CDSS). The clinical decision support will receive blood pressure measurements information every two to four weeks (either manually by the CHW/Nurse team in Intervention (CHW) or via direct cellular data transfer in Intervention (eCHW+)). The CDSS will be designed to make treatment recommendations based on the participants blood pressure measurements, prior drug reaction history if any, and current treatment status in accordance with the South African Hypertension guidelines in use in the PCCs in KZN. Additionally, if any laboratory tests are recommended based on the guidelines, the CDSS will also recommend these tests be done.

b. **Data Protection and Confidentiality**

Paper forms that include participant protected health information will be stored on the day of enrollment in participant specific folders within locked file cabinets in locked research offices. Only study staff will have access to the file cabinets. All other study data will be free of identifying information. Data will be stored on an encrypted REDCap Server hosted by the Africa Health Research Institute. Access to the study database both on site and remotely is restricted to study staff and password protected. All study mobile tablets will be password protected and encrypted prior to study initiation. Data collected on mobile tablets will be uploaded to the server in real-time during data entry or synced to the server as soon as data/Internet access becomes available if it is not during data entry, using the REDCap Offline Application.

c. **Specimen Collection and Testing**

A single blood specimen will be collected in this study at enrollment for renal function assessment to determine eligibility and help guide therapy. Participants will receive a point-of-care creatinine (Cr) using a lancet for finger-stick blood collection to evaluate renal function which can be used for study eligibility and initiation of certain therapies depending on normal renal function. No additional blood or specimens will be collected as part of the trial.

d. **Data Monitoring and Quality Control**

Study data coordinators will perform routine reviews of data quality to identify unusual values and missing data entries. Initial analyses will include common exploratory data analyses, table construction, and scatterplots to assist in data quality control, randomization balance, and exploring for possible outliers. A data flow map will be developed to describe the process for data flow from the home to the nurses and the CDSS and back to the CHWs and then back to the participant's home in repeating cycles in Intervention (CHW) and (eCHW+). Additional checks will be in place for data coordinators to assess face validity of key indicators such as blood pressure measurements and medication prescriptions.

I. Study Monitoring and Regulatory Oversight

a. **Staff Training**

i. **Research Staff:**

All research assistants will complete training through the CITI biomedical human subjects research course or a refresher course, as indicated. Only research staff fluent in the local languages (IsiZulu) will conduct informed consent and survey procedures. Study staff certified in phlebotomy will complete any blood collection procedures. Study staff will maintain active research ethics certification and attend any annual research ethics conferences as mandated by local policy at their institutions.

ii. Clinical Study Staff:

Prior to study initiation, clinical study staff will complete a training in the interpretation of blood pressure and CDS treatment recommendations and hypertension guidelines. The course will be designed and directed by study Co-Investigators Drs. Thomas Gaziano, Shafika Abrahams-Gessel and Dr. Nambulelo Magula and conducted at the study sites. The course will include a review of CVD, HTN, major HTN drug classes, side-effects and a case-based learning session.

b. Regulatory Oversight and Safety Monitoring

Study protocols will be submitted for review to the University of KwaZulu-Natal Biomedical Research Ethics Committee and the Institutional Review Board of Massachusetts General Brigham. The protocol will also be submitted for registration at Clinicaltrials.gov. All protocol amendments, adverse events, unexpected events, and data monitoring review activities will also be submitted to each of these regulatory authorities per the guidelines.

i. Safety Monitoring:

The study co-principal investigators will be ultimately responsible for study conduct, safety, reporting, and interactions with regulatory authorities. Study PIs will ensure: 1) proper conduct of the informed consent process (e.g. that informed consent is obtained before proceeding with study procedures); 2) goal enrollment of study subjects; 3) adequate and high-quality collection and analysis of data; 4) the implementation of study procedures in accordance with study standard operating procedures in order to ensure monitoring of subjects for possible adverse events; 5) prompt review and response to adverse and unexpected events, and reporting to IRBs; and 6) maintenance of the privacy and confidentiality of study subjects. The PIs will be in contact with the research team on a regular basis to review the progress of the study and address any human subject issues that occur. These discussions may involve adverse event prevention measures, recruiting of appropriate study subjects, research staff training on protection of human subjects, as well as occurrence of adverse events, unexpected incidents, or protocol problems.

Finally, the study statistician and co-investigators will meet annually to perform the following activities: a) review the research protocol and plans for data and safety monitoring; b) review progress of the trial, including analysis of data quality and timeliness; subject recruitment, randomization and retention; subject risk versus benefit; and other factors that may affect outcome. c) review serious and unexpected adverse event reports, provide commentary, and provide oversight to ensure that reports are relayed to individual IRBs; d) review proposed modifications to the study prior to their implementation.

ii. Adverse and Unexpected Event Reporting:

To identify adverse events: (1) study clinicians will perform a clinical review at each study

visit and (2) study staff will instruct participants to report any unexpected or severe adverse events to their assigned research assistant. Such a report will immediately be brought to the attention of study principal investigators. Any adverse events that are unanticipated (i.e., not related to standard HTN clinical care or thought to be directly related to study procedures) or severe (e.g. death) will be recorded on an adverse events log form and brought to the attention of the principal Investigator, as well as be reported to participating ethical review committees within 7 days. The relevant committee will determine whether it is appropriate to pause the study or alter the study protocol and will provide suggestions/modifications to the study procedures as necessary. Possible modifications include adding adverse events to the consent form and re-consenting all study participants. The site principal investigator will be responsible for monitoring participant safety at each site on a monthly basis at regularly scheduled research meetings. They will keep a written log of all events and ensure that the ethical review committee is contacted when necessary. They will also keep a log of the outcome of committee decisions regarding adverse events and apprise the research team of any changes that need to occur as a result of such decisions.

J. Statistical Considerations and Analyses

a. Sample Size

Based on prior studies we anticipate a mean blood pressure of 150/95 mmHg among randomized participants with a standard deviation of 19 mmHg [5]. To detect a 5 mmHg difference between arms in the change of blood pressure from baseline to 6 months, we will need to enroll 774 participants (258 per arm) to provide 80% power, assuming 20% loss to follow-up, a correlation between baseline and follow-up measurements of 0.5, and an alpha of 2.5% to account for multiple testing with comparison between the SOC and both intervention arms (**Table 2**). This same sample size will also give us greater than 80% power to detect an increase in the proportion of participants who achieve BP control (defined by a systolic BP <140 mmHg and diastolic BP <90mm Hg) at 6 months from 30% in the SOC arm to 45% in the interventions arms, or from 40% in the SOC to 56% in the intervention, also allowing for an alpha of 2.5% to account for multiple testing. We estimate that there are over 2,500 individuals to draw this sample from within our catchment area served by the three most heavily population primary care clinics in the catchment area (**Table 3**).

Table 2. Differences in change from baseline that can be detected with 80% power

330	264	5.0	19.0	0.20	80%
258	206	5.0	19.0	0.50	80%
148	118	7.5	19.0	0.20	80%
115	92	7.5	19.0	0.50	80%

Table 3. Hypertension visits and patients at clinics in the study catchment area (2020)

Clinic	Hypertension Visits	Patients with Hypertension	Patients with Uncontrolled Hypertension
Esiyembeni	458	152	163
Gunjaneni	1481	424	245
Hluhluwe	1010	406	828
KwaMsane	1997	768	168
Machibini	1692	428	7
Madwaleni	814	406	507
Mpukunyoni	1277	569	63
Mtubatuba	1089	545	36
Nkundusi	1392	465	578
Ntondweni	869	288	163
Somkhele	1685	652	245
Totals	13764	5103	2595

K. Study Outcomes

- a. **Primary Outcome of Clinical Trial:** Difference between arms in change from baseline in systolic blood pressure (SBP) 6 months after enrollment.
- b. **Secondary Outcomes:**
 - Proportion with blood pressure control at 6 after enrollment (<140/90 mmHg).
- c. **Safety Measures:**
 - Number of adverse drug reactions.
 - Proportion of participations retained in hypertension care at 6.

L. Aim 2 Analysis Plan

We will summarize participant sociodemographic and clinical characteristics at baseline in all three arms. We will use linear regression to estimate the difference between arms, and its 95% confidence interval (CI), in systolic blood pressure at 6 months, adjusted for baseline systolic BP. We will use logistic regression to estimate odds ratios (OR) and 95% CIs for the impact of the intervention on the proportion of participants who achieve blood pressure control (<140/90) at 6 months.

Characteristics of individuals who are lost to follow-up will be tabulated by study arm. Since study nurses will visit all participants at home to measure blood pressure at 6 and 12 months, we do not expect there to be differential loss to follow-up between arms. In the primary analyses, participants with missing data at 6 months will be excluded. In sensitivity analyses, those with missing measurements will be considered to have no change in systolic BP and uncontrolled BP. Missing values may also be imputed using multiple imputation.

In pre-planned secondary analyses, we will fit regression models stratified by sex (to assess for sex as a biologic variable), age strata, socioeconomic status and baseline co-morbidities (i.e. obesity and HIV) to determine sub-group effect sizes and test the significance of an interaction term between sub-groups and the intervention to assess for effect modification.

A detailed statistical analysis plan will be prepared before the data are examined by treatment arm.

M. Risks, Protection from Risks and Benefits to Study Participation in Aim 2

a. Risks and Protections

- i. One risk to participation is breach of confidentiality. Study staff will be trained in confidentiality and all staff members will be required to sign confidentiality agreements. Assurance of privacy in testing and communication of results will be done. Quality assurance processes will include regular support/supervision visits in the field and self-evaluations in this study. To ensure confidentiality of participants, all data will be coded by subject number. Data recorded on paper will be kept in locked cabinets with access only by members of the research team. There will be strict limited access to electronically stored data as well, using password protection. Research records will be kept confidential following national regulations. The subject's name or other personal identifiers will not be included with specimens sent to the laboratory, which will be identified only by a code number. Interviewers and support staff will be trained on procedures for maintaining confidentiality.
- ii. We will conduct a single specimen collection during this study to conduct point of care creatinine testing that will be administered by trained study staff. A trained nurse will collect blood from a pin prick using standard precautions requiring only up to 2 drops of blood (< 1ml) to be drawn.
- iii. Study participants in both the SOC and intervention arms with uncontrolled hypertension will receive one of four blood pressure medications on the South African Essential Medication list according to the local guidelines including: hydrochlorothiazide, enalapril or other angiotensin converting enzyme inhibitor, amlodipine, or a beta-blocker. No experimental medications will be used. Participants will be followed for side-effects in accordance with the South African hypertension guidelines by the nurses and the CHWs. All participants who experience any adverse event will receive follow-up until adverse event is resolved by the local study staff. Severe and serious adverse events will be documented and reported to the involved regulatory bodies per their regulations.
- iv. A secondary risk of participation in this Aim is loss of time from participation in interviews and/or discomfort with the questions asked or nature of the conversations. All participation will be voluntary and participants will be free to pause, interrupt, or not respond to any questions or content areas that make them uncomfortable.
- v. Participants in the CHW and eCHW+ arms of the study have a risk of receiving less than the standard of care by not attending the clinic, particularly if data from the home blood pressure cuffs are not being transmitted manually or automatically to the clinical decision support system. Protections will be in place such that the nurses who remain the backbone of hypertension care in all intervention and control clinics will have the ability to communicate with the CHW to ensure a) blood pressure data is transmitted properly or faulty equipment is repaired or replaced, b) prescriptions are available for patients or delivered as allowed, or c) communicate through the CHWs so that the participant can come in for a visit or make a home visit to ensure that care consistent with guidelines is available to all participants.

b. Benefits

- i. Participants may lead to a reduction in their blood pressure level and overall improved blood pressure control. Participants in the intervention arm may develop proficiency in managing

their own blood pressure and learning about the operation of a home blood pressure device.

- ii. Participants may gain a better understanding of their cardiovascular risk profile. Any identified with having advanced renal disease may be referred for additional care and therapy.
- iii. Some participants might gain a personal sense of pride from knowing they are contributing to development of a system that intends to improve hypertension care in their community, or for the opportunity to contribute to its design.
- iv. If one of the interventions is ultimately successful, this study might provide a benefit to the community by helping to guide development of an improvement system of hypertension care.
- v. A financial incentive of R150 will be paid to participants for participation in the clinical trial. An incentive of R50 will be given after each study visit at baseline, month 6 and month 12.

VI. AIM 3

Determine the fidelity, sustainability, acceptability, and cost-effectiveness of community-based, technology-supported hypertension interventions to reduce blood pressure in rural KwaZulu-Natal.

Aim 3 will have two primary components:

(3a) Building on the qualitative research conducted before and early in the trial, we will conduct additional qualitative research to assess the acceptability of the interventions and quantitative monitoring of implementation throughout the trial to assess fidelity and sustainability.

(3b) We will record the costs of care and of the interventions and determine the cost-effectiveness of the intervention with microsimulation model (CVD PREDICT) that uses individual-level risk factor data and health cost inputs.

A. Methods

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

The use of the CMIR and TFA (Aim 1) will be extended to evaluate the overall acceptability, fidelity, and sustainability of the intervention.

Approximately 12 months after the start of the trial we will conduct key informants interviews and individual interviews with health workers and trial participants. Where appropriate we will include the same individuals sampled for Aim 1, to compare their experiences during the trial with their initial expectations and preferences. Qualitative data collection and analysis will be similar to Aim 1 methods, adapted as necessary to accommodate unforeseen issues that arise during the trial.

Study documentation (e.g. coordination meeting minutes, supervision visit reports) will be reviewed to extract any relevant information contributing to document adaptations to implementation, and thereby fidelity, decision-making process and thereby acceptability (and feasibility), and short-term sustainability.

These qualitative data will be complemented by collection of quantitative indicators of fidelity and sustainability of implementation. An assessment of the intervention's fidelity will be performed 6 and 12 months after study enrollment (based on monthly data collection), while sustainability will be measured at the 12-month visit. Data will be collected through repeated completion of intervention fidelity clinic checklists to estimate adherence, exposure, and quality of the intervention.

b. (Aim 3b) Cost-effectiveness

Cost-effectiveness of the intervention compared to standard of care in blood pressure management, will be calculated as incremental costs for absolute changes in blood pressure (costs/mmHg) and incremental costs per extra participant with controlled blood pressure. The Harvard CVD PREDICT microsimulation model for cost-effectiveness and changes in CVD-related health outcomes will be used to conduct this analysis. The cost-effectiveness will be calculated across the entire intervention, as well as separately by each of the study arms.

B. Study Outcomes

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

Study outcomes measuring acceptability, fidelity, and sustainability of the intervention are summarized below in **Table 4**.

b. (Aim 3b) Cost-effectiveness

- Costs to participants of health care including (where applicable) the interventions
- SBP reduction and blood pressure control resulting from the interventions
- Quality adjusted life years (QALYs)
- Incremental cost-effectiveness ratios (ICERs), that is, incremental cost per mmHg SBP reduction, per extra participant with controlled blood pressure, and per QALY gained as effects of the interventions

Table 4. Summary of acceptability, fidelity, and sustainability outcome measures for Aim 3a

Category	Study Outcomes	Source/Measurement
Acceptability	- Participant and provider perception of the intervention and clinical decision support tools.	- Key informants interviews. - Individual interviews.
Fidelity	- Proportion of successful and failed BP data transmission events, among all transmitted BP data events.	
	- Proportion of CDS-recommended treatment changes initiated by nurse/CHW, among all CDS-recommended treatment changes.	
	- Number of BP cuffs distributed to participants in 2 intervention arms.	- Study check lists.
	- Number of BP readings manually recorded by intervention participants.	- CDS records.
	- Number of CHWs trained on HBPM and data tool input/management.	- Study check lists.
Sustainability	- Number of participants with treatment initiation during study period.	- Participant study records. - Outreach team leader supervision records.
	- Number of BP cuff training sessions provided to participants at home by CHWs.	- CHW study records.
	- Number/frequency of CHW home visits conducted versus planned	- CHW study records
	- Number of participants counseled in lifestyle modification and medication adherence at home by CHWs. => Fidelity?	- CHW study records.
	- Number of clinics adopting use and distribution of BP cuffs for HBPM.	- Study check lists.
	- Proportion of clinics sustaining use and distribution of BP cuffs for HBPM at 12 months, among those who distributed BP cuffs at the start of the study.	- Study check lists.
	- Proportion of participants retained in hypertension care at 12 months, among enrolled study participants.	- Participant study records.
Sustainability	- Absolute change in systolic blood pressure (SBP) between 6 and 12 months after enrollment, among enrolled study participants.	- CDS records
	- Proportion of participants retained in hypertension care at 12 months, among enrolled study participants.	- Participant study records.
	- Absolute change in systolic blood pressure (SBP) between 6 and 12 months after enrollment, among all study participants.	- CDS records.

C. Data Sources

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

Both the fidelity and the sustainability of the intervention will be assessed using data obtained through review of study check lists, the participant study records (including prescriptions), CDS records, CHW study records, outreach team leader supervision records, and coordination meeting minutes.

Key informant and individual interviews will assess overall acceptability and experience of the intervention.

b. (Aim 3b) Cost-effectiveness

Cost data will be obtained from trial participant interviews, KZN DoH unit prices, and analysis of intervention delivery.

The trial will provide individual level outcome data on SBP and blood pressure control 6 and 12 months. The PREDICT model will use these data to predict long term effects of the interventions on quality adjusted life years (QALYs)

D. Recruitment

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

As appropriate, for key informants and individual interviews, we will try to recruit from the same sample used in Aim 1 in order obtain maximal information about changes in expectations and experiences before and after the trial. Key informants will be identified and contacted by study investigators at AHRI from current and prior collaborators working on improving health care in this rural population. Health care workers will be identified from personnel records at the study clinics and be invited to participate in interviews by study investigators. Participants will be identified from clinic registers for hypertensive patients.

b. (Aim 3b) Cost-effectiveness

Participants will not be enrolled for this part of Aim 3 and cost data will be obtained as described in Section C(b) above.

E. Enrollment

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

i. Inclusion Criteria for Key Informants

- age 18 and over.
- representative of the KZN DoH for involved in management of primary care delivery programs.

ii. Inclusion Criteria for Health Care Workers

- age 18 and over.
- currently employed as a health care worker (physician, nurse, CHW, pharmacist, clinic administrator/operational manager) at one of the study clinics.

iii. Inclusion Criteria for Participants

- age 18 and over.
- diagnosed with uncontrolled hypertension.

- selection based on pre-defined criteria such as age, gender, trial arm, patients accepting/refusing the intervention.

- b. (Aim 3b) Cost-effectiveness
Not applicable

F. Sample Size

- a. (Aim 3a) Fidelity, Sustainability, and Acceptability
- Key informants interviews: minimum 5
 - Interviews with professional health care workers: minimum 15 (3 per facility), including chronic nurse, OM, nurse “supervising” CHW, doctors maybe (supervisory role)
 - Interviews with CHW (minimum 3 per clinic)
 - Interviews with patients: minimum 15
- b. (Aim 3b) Cost-effectiveness
All trial participants will be included in analysis of costs and cost effectiveness.

G. Informed Consent

- a. (Aim 3a) Fidelity, Sustainability, and Acceptability
As in Aim 1, key informant discussants will be invited to participate in discussions about the planned study and their participation in meetings will be taken as consent to participate.
Study research assistants will recruit participants enrolled in the study and health care workers to participate in the focus groups.

Persons who participated in Aim 1 activities and who will participate in Aim 3 activities, will be reconsented regardless of whether they provided verbal or written consent in Aim 1. Consenting procedures for Aim 3 will be identical to those described in Aim 1.

- b. (Aim 3b) Cost-effectiveness
This will be included in the consent to participate in the trial.

H. Data Collection

- a. (Aim 3a) Fidelity, Sustainability, and Acceptability
Data on fidelity outcomes will be obtained from study checklists and data collected with the electronic hypertension management tool in the intervention arms at 6 and 12 months. Sustainability measures, including changes in systolic blood pressure, will be collected using the same sources at 12 months in the intervention arms. In the standard of care arm changes in systolic blood pressure at 12 months and medication use will be obtained through participant chart reviews. All data will be combined into a database for analyses and all personal identifiers will be removed prior to analysis.
Interviewers will use guides with open-ended questions to collect qualitative data on the overall acceptability of the intervention.
- b. (Aim 3b) Cost-effectiveness
Resource allocation assessments in all three study arms will be conducted at 6 and 12

months after the start of the trial using a time and motion study over five clinic days, along with medical records reviews and participant exit interviews. Using these measurements, the public-sector unit costs for managing hypertension will be calculated, including human resources, diagnostics and supplies, therapeutics, and home blood pressure monitors. Costs will be collected from relevant sources, including clinic sites, the South African Department of Health, and published reports. A societal perspective will be applied to data collection and analysis.

I. Analysis

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

Quantitative data will be analyzed using Stata Statistical Software (Release 17. College Station, TX) and statistics for fidelity and sustainability outcomes will be generated. Qualitative data analysis will be performed using similar methods as in Aim 1. The key informants and individual interviews will be collected in isiZulu, then transcribed, and translated in English by a team of social science research assistants. A data-led coding framework will be developed, based on themes, which emerge from the data. The research assistants involved in collecting the data will work with other social science team members to agree on the coding framework and performing coding of the data. Thematic summaries will be prepared using the data and a process of building consensus among the whole study team. These summaries will form the building blocks for reporting the findings. Organization of data on the acceptability of the intervention will again be organized into component constructs using the Theoretical Framework for Acceptability, as described in Aim 1.

b. (3b) Cost and Cost-effectiveness

Cost-effectiveness of the intervention compared to standard of care in blood pressure management, will be calculated as incremental costs for absolute differences in blood pressure (costs/mmHg) and incremental costs per extra participant with controlled blood pressure. This analysis will be performed using the Harvard CVD PREDICT model [15] for cost-effectiveness and changes in CVD-related health outcomes. The model will be used to assess the cost-effectiveness of the intervention and to model the impact on the observed change in systolic blood pressure on future CVD events. We will also use the model to translate the intervention effectiveness established during the trial into quality adjusted life years (QALY) and applying assumptions about effects of SBP reductions on survival, quality of life, and complications, based on the extant literature and confirmed locally as part of this trial.

The cost-effectiveness will be calculated across the entire intervention, as well as separately by each of the study arms and expressed in incremental cost-effectiveness ratios (ICERs) and quality adjusted life years (QALYs).

If there is a significant reduction in SBP, we will measure the long term expected reductions in major cardiovascular events and mortality in the population beyond the study period, and for a nationally scaled population. For these predictive cost-effectiveness analyses, we will assess the costs and cost-effectiveness of the intervention modeling the impact on the change in SBP on future CVD events.

Health-related quality of life is measured using the time trade off approach for a reference population in sub-Saharan Africa as adopted in similar cost-effectiveness analyses. We will conduct probabilistic sensitivity analysis by defining probability distributions of variables in the model used to calculate the costs and effectiveness.

We will develop the cost-utility model using best practices outlined by the ISPOR Good Research Practice Task Force [16-19] and guidelines set out by the US Second Panel on Cost-Effectiveness in Health and Medicine.

J. Risks, Protection from Risks and Benefits to Study Participation in Aim 3a and 3b

- a. Risks and Protections
 - i. The primary risk to participation is breach of confidentiality. We will not record names of any individuals taking part in interviews, nor will we report them in findings to be disseminated as part of this project. Given the low number of people in the study and the identification of participants (e.g., stakeholders in the Department of Health) it is possible that their identities could be inferred and we will make this risk clear during the consenting process.
 - ii. A secondary risk of participation in in this aim is loss of time from participation in interviews and/or discomfort with the questions asked or nature of the conversations. All participation will be voluntary and participants will be free to pause, interrupt, or not respond to any questions or content areas that make them uncomfortable.
- b. Benefits
 - i. Most study participants in Aim 3 will derive no direct benefit from participation in the study.
 - ii. Some participants might gain a personal sense of pride from knowing they are contributing to development of a system that intends to improve hypertension care in their community, or for the opportunity to contribute to its design.
 - iii. If one of the interventions is ultimately successful, this study might provide a benefit to the community by helping to guide development of an improvement system of hypertension care.
 - iv. The cost-effectiveness analysis will provide insight for policy makers into whether the proposed interventions is a good use of health care resources for reducing the disease burden of uncontrolled hypertension substantially in the new community based primary care model.
 - vi. A financial incentive of R50 of airtime (telephonic), R50 in cash (in-person), or a R50 food voucher will be provided to participants for their participation in discussion groups and interviews, subject to COVID-19 restrictions in place.

VII. REFERENCES

1. O'Donnell, MJ, Chin, SL, Rangarajan, S, *et al.* Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016;388(10046):761-75.
2. Nojilana, B, Bradshaw, D, Pillay-Van Wyk, V, *et al.* Emerging trends in non-communicable disease mortality in South Africa, 1997 - 2010. *S Afr Med J.* 2016;106(5):58.
3. Lim, SS, Vos, T, Flaxman, AD, *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2224-60.
4. Mills, KT, Bundy, JD, Kelly, TN, *et al.* Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation.* 2016;134(6):441-50.
5. Wong, EB, Olivier, S, Gunda, R, *et al.* Convergence of infectious and non-communicable disease epidemics in rural South Africa: a cross-sectional, population-based multimorbidity study. *Lancet Glob Health.* 2021;9(7):e967-e76.
6. South African National Department of Public Health. Strategic Plan 2020/21-2024/25 (RP: 108/2020) Available at: <http://www.hsrc.ac.za/uploads/pageContent/3893/NCDs%20STRAT%20PLAN%20%20CONTENT%208%20april%20proof.pdf>. 2019.
7. KwaZulu-Natal Department of Public Health. STRATEGIC PLAN 2020/21 – 2024/25. Available at: <https://www.kznhealth.gov.za/Strategic-plan-2020-2025.pdf>. 2019.
8. Iwuji, CC, Orne-Gliemann, J, Larmarange, J, *et al.* Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial. *Lancet HIV.* 2017.
9. World Health Organization (Who). Community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic: interim guidance, May 2020. World Health Organization; 2020.
10. South African National Department of Public Health. Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013-17 Available at: <http://www.hsrc.ac.za/uploads/pageContent/3893/NCDs%20STRAT%20PLAN%20%20CONTENT%208%20april%20proof.pdf>. 2013.
11. Proctor, E, Silmere, H, Raghavan, R, *et al.* Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health.* 2011;38(2):65-76.
12. Sekhon, M, Cartwright, M, Francis, JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Services Research.* 2017;17(1):88.
13. O'mara-Eves, A, Brunton, G, Oliver, S, *et al.* The effectiveness of community engagement in public health interventions for disadvantaged groups: a meta-analysis. *BMC Public Health.* 2015;15(1):129.
14. World Health Organization (Who). WHO STEPS surveillance manual: the WHO STEPwise approach to chronic disease risk factor surveillance. World Health Organization; 2005. Report No.: 9241593830.
15. Pandya, A, Sy, S, Cho, S, *et al.* Validation of a Cardiovascular Disease Policy Micro-Simulation Model using Both Survival and Receiver Operating Characteristic Curves. *Med Decis Making.* 2017:272989x17706081.
16. Briggs, AH, Weinstein, MC, Fenwick, EA, *et al.* Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. *Value in Health.* 2012;15(6):835-42.

17. Caro, JJ, Briggs, AH, Siebert, U, *et al.* Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. *Value Health.* 2012;15(6):796-803.
18. Mauskopf, JA, Sullivan, SD, Annemans, L, *et al.* Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. *Value Health.* 2007;10(5):336-47.
19. Neumann, PJ, Sanders, GD, Russell, LB, *et al.* *Cost-effectiveness in health and medicine:* Oxford University Press; 2016.

Final Trial Protocol

IMPACT-BP:

Implementation of a Combination Intervention for Sustainable Blood Pressure Control in Rural
KwaZulu-Natal, South Africa

Version 5: February 15, 2024

Africa Health Research Institute
Brigham and Women's Hospital
Massachusetts General Hospital

ABBREVIATIONS

AHRI	Africa Health Research Institute
ART	Antiretroviral therapy
BP	Blood pressure
CBPM	Community Blood Pressure Monitor
CHW	Community Health Worker
CDS	Clinical Decision Support
CMIR	Conceptual Model of Implementation Research
CKD	Chronic Kidney Disease
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DBP	Diastolic blood pressure
DM	Diabetes Mellitus
DoH	Department of Health
GFR	Glomerular Filtration Rate
HBPM	Home-based Blood Pressure Management
HTN	Hypertension
ICERs	Incremental cost-effectiveness ratios
KZN	KwaZulu-Natal
MI	Myocardial infarction
NCD	Non-communicable disease
NHLBI	National Heart, Lung, and Blood Institute
PCCs	Primary care clinic(s)
PHC	Primary health center
POC	Point of care
SA	South Africa
SBP	Systolic blood pressure
SOC	Standard of care
SOP	Standard operating procedure
QALYs	Quality adjusted life years

TABLE OF CONTENTS

I.	INVESTIGATORS AND INSTITUTIONS	42
II.	STUDY FUNDING AND REGISTRATION	43
III.	PROJECT SUMMARY AND SPECIFIC AIMS	44
IV.	AIM 1: READINESS AND ACCEPTABILITY ASSESSMENT	46
A.	Methods	46
B.	Study Outcomes	47
C.	Eligibility Criteria Rationale	47
a.	Key Informants	47
b.	Health Workers	47
c.	Patients/Eligible Study Participants	47
D.	Recruitment	47
E.	Enrollment	47
a.	Inclusion Criteria for Key Informants	47
b.	Inclusion Criteria for Health Care Workers	47
c.	Inclusion Criteria for Participant Focus Groups	48
F.	Sample Size	48
G.	Informed Consent	48
H.	Data Collection and Analysis	48
a.	Data Collection	48
b.	Data Analysis	48
I.	Risks, Protection from Risks and Benefits to Study Participation in Aim 1	49
a.	Risks and Protections	49
b.	Benefits	49
V.	AIM 2: IMPLEMENTATION CLINICAL TRIAL	50
A.	Aim 2 Overview	50
	Figure 1. Study Schema	50
B.	Eligible Study Population	51
C.	Eligibility Criteria	51

a.	Inclusion Criteria	51
b.	Exclusion Criteria	51
D.	Subject Recruitment	51
a.	Participant Identification	51
E.	Informed Consent	52
F.	Randomization	52
G.	Aim 2 Study Procedures	52
a.	Blood Pressure Monitoring Procedures by Study Arm.....	52
i.	SOC: Baseline Visit for Clinic-Based Standard of Care Participants (Figure 2)	52
ii.	Intervention 1: Community Blood Pressure Monitor Model (CBPM) (Figure 3).....	53
iii.	Intervention 2: Enhanced Community Blood Pressure Monitor-based with mobile health blood pressure monitoring model (eCBPM+) (Figure 4)	54
b.	Study Visit Schedule	55
i.	Visit 1: Enrollment.....	55
ii.	Visit 2: 6-month BP Measurement Assessment and Medication Use	55
iii.	Visit 3: 12-month BP Measurement Assessment and Evaluation of BP Device Function...	55
iv.	Extension phase and additional study visits: 18 and 24-month BP Measurement Assessment and Evaluation of BP Device Function	56
v.	Missing and Late Appointments.....	56
	Table 1. Summary of Study Visit Procedures.....	56
H.	Data Systems and Management	56
a.	Data Systems.....	56
i.	REDCap Study Database	56
ii.	Hypertension Management Application	57
b.	Data Protection and Confidentiality.....	57
c.	Data Sharing	57
d.	Specimen Collection and Testing	57
e.	Data Monitoring and Quality Control	58
I.	Study Monitoring and Regulatory Oversight	58
a.	Staff Training.....	58
i.	Research Staff	58
ii.	Provider Staff	58
b.	Regulatory Oversight and Safety Monitoring	58
i.	Safety Monitoring:	58
ii.	Adverse and Unexpected Event Reporting:	59
J.	Statistical Considerations and Analyses.....	59
a.	Sample Size.....	59
	Table 2. Differences in change from baseline that can be detected with 80% power	60
	Table 3. Hypertension visits and patients at clinics in the study catchment area (2020).....	60
K.	Study Outcomes	60

a.	Primary Outcome of Clinical Trial:	60
b.	Secondary Outcomes:	60
c.	Safety Measures	60
L.	Aim 2 Analysis Plan.....	61
M.	Risks, Protection from Risks and Benefits to Study Participation in Aim 2	61
a.	Risks and Protections	61
b.	Benefits	62
VI.	AIM 3	63
A.	Methods	63
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability.....	63
b.	(Aim 3b) Cost-effectiveness.....	63
B.	Study Outcomes	64
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability.....	64
b.	(Aim 3b) Cost-effectiveness.....	64
	Table 4. Summary of acceptability, fidelity, and sustainability outcome measures for Aim 3a.....	65
C.	Data Sources	66
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability.....	66
b.	(Aim 3b) Cost-effectiveness.....	66
D.	Recruitment.....	66
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability.....	66
b.	(Aim 3b) Cost-effectiveness.....	66
E.	Enrollment	66
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability	66
i.	Inclusion Criteria for Key Informants	66
ii.	Inclusion Criteria for Health Care Workers.....	66
iii.	Inclusion Criteria for Participants	66
b.	(Aim 3b) Cost-effectiveness.....	67
F.	Sample Size	67
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability.....	67
b.	(Aim 3b) Cost-effectiveness.....	67
G.	Informed Consent	67
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability.....	67
b.	(Aim 3b) Cost-effectiveness.....	67
H.	Data Collection.....	67
a.	(Aim 3a) Fidelity, Sustainability, and Acceptability.....	67
b.	(Aim 3b) Cost-effectiveness.....	67

I. Analysis 68
a. (Aim 3a) Fidelity, Sustainability, and Acceptability..... 68
b. (3b) Cost and Cost-effectiveness..... 68

J. Risks, Protection from Risks and Benefits to Study Participation in Aim 3a and 3b..... 69
a. Risks and Protections 69
a. Benefits 69

VII. REFERENCES 70

I. INVESTIGATORS AND INSTITUTIONS

Thomas A. Gaziano, MD MSc
Harvard Medical School
Tel: +1-617-432-4348

Co-Principal Investigator
Massachusetts General Brigham
Email: tgaziano@bwh.harvard.edu

Mark J. Siedner, MD MPH
Harvard Medical School
Tel: +1-617-726-4686

Co-Principal Investigator
Massachusetts General Brigham
Email: msiedner@mgm.harvard.edu

Max Bachmann, MD PhD MSc
Norwich Medical School
Tel: +44 (0)1603-59 1220

Co-Investigator
University of East Anglia
Email: M.Bachmann@uea.ac.uk

Nombulelo Magula,
MBChB, MSc, FCP(SA), PhD
Nelson R Mandela School of Medicine
Tel: +27 31 260 4238

Co-Investigator
University of KwaZulu-Natal
Email: magulan@ukzn.ac.za

Joanna Orne-Gliemann, PhD MPH
Bordeaux University
Tel: +33 (0) 5.57.57.45.17

Co-Investigator
Email: Joanna.Orne-Gliemann@u-bordeaux.fr

II. STUDY FUNDING AND REGISTRATION

Sponsor: National Heart, Lung, and Blood Institute (NHLBI)

Grant Number: NIH R01 HL144848

FAIN: R01HL144848

Study Period: September 04, 2020 – August 31, 2025

ClinicalTrials.gov registration Number: NCT05492955

III. PROJECT SUMMARY AND SPECIFIC AIMS

Uncontrolled hypertension is the primary risk factor for stroke and hypertensive heart disease, which are the leading causes of non-communicable disease (NCD) deaths in South Africa, and of disability adjusted-life years lost globally [1-3]. Yet, there is a large knowledge-implementation gap between efficacy literature on hypertension control and effectiveness of health systems to provide hypertension care [4]. This is particularly true in resource-limited settings. In rural KwaZulu-Natal (KZN), we recently found that approximately one in six adults over 18 years old have hypertension, and fewer than one in four of those with hypertension have disease control [5].

The South African (SA) Department of Health (DoH) in its “Strategic Framework 2019-2024” has set a goal to increase life-expectancy through universal health coverage [6]. KZN Health has outlined its strategic goals to be consistent with the National goals to reduce morbidity and mortality through increased screening, treatment, and control of NCDs [7]. These goals will be achieved through an enhanced community-based care program, that will further integrate community health workers (CHWs) into the public health system, strengthen clinics, and implement a digital health strategy. The basic structure of the community-based program is the linkage of Ward Based Primary Care Outreach teams that are linked to the primary health center (PHC) facility and consists of a team of CHWs lead by an outreach team leader who is a trained nurse. The COVID-19 pandemic has accelerated the need for these changes which would allow community members to receive a greater portion of their care in their homes limiting overcrowding of clinics and decreasing infection risk.

The scientific goals of this project are to inform best practices for implementation of interventions targeting health systems and individual barriers to effective hypertension care in rural KwaZulu-Natal. We have selected a combination of interventions, effective in clinical trials but without widespread successful health system translation in resource-limited settings, that target both the health system and the individual to attain improved blood pressure control. Our intervention design specifically reflects support for community-based delivery of care for chronic diseases, that has been established to be effective in HIV care [8], increasingly prioritized in light of the COVID-19 pandemic [9] and is promoted by the South Africa Department of Health Non-Communicable Disease Control Program Policy Statements [10]. We will conduct a randomized trial to evaluate community-based hypertension control programs based on three primary components: a) community-based disease management with home-blood pressure measurements; b) a nurse champion for program oversight, and c) use of a clinical decision support system. Community blood pressure monitors (CBPMs) will be employed to execute study activities, in a capacity that is equivalent to that of CHWs in the DoH Ward Based Primary Care Outreach teams.

We will evaluate the implementation of two community-based, technology-supported programs to improve blood pressure control in South Africa, guided by the Conceptual Model for Implementation Research [11], with a focus on acceptability (Aim 1), effectiveness (Aim 2) and feasibility, cost- effectiveness and sustainability (Aim 3). We will leverage a 20-year partnership with the Department of Health, a multidisciplinary team of experts, and a recent health screening of approximately 18,000 individuals in the catchment area [5] to accomplish the above goals, and to accomplish the following aims:

Aim 1

Evaluate the acceptability and conduct a readiness assessment for implementation, of community-based hypertension, technology-supported interventions to reduce blood pressure in rural.

Guided by the Conceptual Model of Implementation Research (CMIR), we will use mixed methods to assess organizational, healthcare worker, and participant readiness for implementation of the interventions. We will use results of the readiness assessments to refine final implementation strategies for the intervention.

Aim 2

Determine the effectiveness of a community-based, technology-supported intervention to reduce systolic blood pressure and increase blood pressure control among individuals with uncontrolled hypertension in rural South Africa.

We will conduct a trial using CBPMs in conjunction with in-home BP monitoring among approximately 774 adults randomized to one of three different arms of hypertension care: 1) clinic-based standard of care model (SOC); 2) community blood pressure monitor-based blood pressure monitoring model (CBPM); 3) and enhanced community blood pressure monitor-based model, including mobile health blood pressure monitoring (eCBPM+).

Aim 3

Determine the fidelity, sustainability, acceptability, and cost-effectiveness of community-based, technology-supported hypertension interventions to reduce blood pressure in rural KwaZulu-Natal.

The use of the CMIR (Aim 1) will be extended to evaluate the fidelity and sustainability of the intervention. A microsimulation model (CVD PREDICT) that uses individual-level risk factor data and health cost inputs will be used to determine the cost-effectiveness of the intervention.

IV. AIM 1: READINESS AND ACCEPTABILITY ASSESSMENT

Evaluate the acceptability and conduct a readiness assessment for implementation, of community-based hypertension, technology-supported interventions to reduce blood pressure in rural KwaZulu-Natal.

A. Methods

Guided by the Conceptual Model for Implementation Research [11] and the Theoretical Framework for Acceptability [12], we will use qualitative methods to assess organizational, healthcare worker, and patient acceptability of and readiness for the implementation of the intervention.

To do so, we will first host a series of key informant interviews and meetings, with representatives from the national DoH and other key stakeholders, which will allow us to assess pre-intervention implementation acceptability and readiness at the organizational level. These interviews/meetings will be designed to assess how the intervention aligns with health policy goals, current practice guidelines and services for hypertension, and institutional resources available to support the project.

Then group discussions will allow us to assess patient, nurse, CHW, and nurse supervisor perceptions about, and acceptability of, the intervention. We will explore areas such as workers' attitudes and beliefs about providing effective care to their patients (including self-efficacy), understanding of the intervention and expected effectiveness, relationships between workers and the primary care system (including perceived burden); we will also investigate patient perceptions of and need for hypertension care provided at the clinics.

These meetings and group discussions will be conducted approximately three months prior to study implementation. This approach allows for in-depth assessment of the initial acceptability of the intervention and to identify potential barriers and facilitators to the intervention and its implementation.

We will conduct selective (purposive) sampling of potential participants at the trial clinics, divided evenly between those who have controlled blood pressure and those who have uncontrolled blood pressure, and include both sexes and a range of ages for maximum variation. Health care workers will be selected from clinics that are included in the study. Participation in the health care worker groups will be determined by role, to encourage participants to share their opinions freely, given the strong hierarchical structure in clinical practice settings.

A major theme of the interviews will be readiness of the system infrastructure to support the intervention will also be assessed through an assessment of the capacity to support the interventions, including available cell phone coverage in the study area, data transfer capacity and processes, and piloting of the blood pressure monitoring app component of the intervention with nurses.

Added support for this intervention will be negotiated with community leadership structures such as the traditional leadership or Ward Councillor. Public health interventions have been shown to have more positive health and psychosocial outcomes when there is community

engagement [13]. This community engagement process will be incorporated into the Conceptual Model for Implementation Research and the Theoretical Framework for Acceptability.

These data will lead to a review the design of the intervention, if relevant, to refine its implementation through adaptations in the randomized clinical trial (Aim 2).

B. Study Outcomes

- Intervention acceptability, readiness, potential barriers and facilitators
- Potential intervention design modifications

C. Eligibility Criteria Rationale

- a. **Key Informants**: partners at the KZN DoH who are familiar with provincial and national health care policies, goals, and systems. These partners will provide important feedback on the alignment and fit of the proposed intervention with the current health priorities, goals, and availability of resources for hypertension care. Community leadership will also be interviewed as key informants in order to assess how the proposed intervention can be supported in community structures.
- b. **Health Workers**: clinic-based professional nurses, operational managers, outreach team leaders, physicians, CHWs, and pharmacists employed at clinics included in the trial. Each of these workers will provide rich data about their experiences providing specific components of clinical care to participants with hypertension, which will help with refining the implementation strategies, including adaptations, for the intervention.
- c. **Patients/Eligible Study Participants**: are expected to be receiving care for hypertension at the clinics included in the trial. Their experiences will be used to identify needs, potential barriers and facilitators to the intervention implementation, which will be considered when designing the implementation strategies of the study.

D. Recruitment

Key informants will be identified and contacted by study investigators at Africa Health Research Institute (AHRI) from current and prior collaborators working on improving health care in this rural population. Health care workers will be identified from personnel records at the study clinics and be invited to participate in the group discussions by study investigators, in agreement with DoH and AHRI policy for conducting research among health care professionals. Participants for group discussions will be identified from clinic registers for hypertensive patients.

E. Enrollment

- d. **Inclusion Criteria for Key Informants**
 - age 18 and over.
 - representative of the KZN DoH for involved in management of primary care delivery programs.
 - Ward Councillor or traditional leadership (Induna) in the community.
- e. **Inclusion Criteria for Health Care Workers**
 - age 18 and over.
 - currently functioning as a health care worker (physician, nurse, CHW, pharmacist,

clinic administrator/operational manager) at one of the study clinics.

f. Inclusion Criteria for Participant Focus Groups

- age 18 and over.
- diagnosed with both controlled and uncontrolled hypertension.

F. Sample Size

Final sample sizes for each of the participant groups will be driven by saturation of themes and in the following ranges:

- Key informants interviews/meetings: 8-10
- Group discussions with health care workers: approximately 2 or until saturation achieved
- (number of participants per group: 8-10)
- Group discussions with patients/eligible future participants: approximately 2 or until saturation achieved
- (number of participants per group: 8-10)

G. Informed Consent

Key informants will be invited to participate in interviews/meetings to discuss about the planned study and their participation will be taken as consent to participate. Study research assistants will recruit participants enrolled in the study and health care workers to participate in the group discussions. The research assistants will explain the activities of the study, how confidentiality will be maintained, and explain the informed consent form, as well as answer any questions. Those who agree to participate will be asked to sign two copies of an informed consent form. One copy will be given to the participant for his/her records and the other will be retained as part of the study record. For those who cannot sign their name, a thumb print will be obtained. If remote participation in group discussions are necessary due to the COVID-19 pandemic restrictions on in-person activities, verbal consent will be obtained and recorded prior to the start of the discussion.

H. Data Collection and Analysis

a. Data Collection

Names of key informants and data from key informants' interviews meetings will be kept confidential and will not be recorded. No personally identifiable data from these meetings will be used in publication or dissemination activities in any form. Data from both study participants and health care workers will be collected from group discussions. A Zulu-speaking research assistant with training in qualitative methods will facilitate the group discussions, which will be held in a private setting to ensure confidentiality and encourage maximum participation. The discussions will be recorded using digital audio. Health care workers and study participants will be asked to complete a short 5-10 item questionnaire and a generic study identification number will be assigned to each person completing the survey. Interviewers and focus group facilitators will use guides with open-ended questions to collect data. Discussions will cover pre-designated core topics such as understanding, perceptions and attitudes towards the planned intervention, any anticipated barriers, and opportunities for implementation.

b. Data Analysis

Group recordings will be transcribed and translated into English. Manual thematic analysis

will be performed using a combination of theory-led (deductive) and data-led (inductive) coding. The study team will collaboratively review the data in both isiZulu and English to identify emerging codes and capture the richness of the data. Research assistants will conduct the primary coding of interview data. Their work will be supervised by at least 2 senior researchers who will perform double coding and review a subset of the research assistants' work to ensure uniformity and quality of the coding process. The senior researchers will review all the coded data and will create thematic summaries. Data management software package (NVivo) will be used to code and explore themes. Data on the acceptability of the intervention will be organized into the seven component constructs of the Theoretical Framework of Acceptability [12], which includes affective attitude, burden, ethicality, intervention coherence, opportunity costs, and perceived effectiveness.

Findings will contribute to identify key areas of the intervention implementation that will need specific attention for effective implementation. These results will be shared with the study team to identify processes in the randomized clinical trial protocol that may need to be adapted prior to implementation. Final training materials for health care workers participating in the trial will be updated to reflect these refinements in implementation.

I. Risks, Protection from Risks and Benefits to Study Participation in Aim 1

a. Risks and Protections

- i. The primary risk to participation is breach of confidentiality. We will not record names of any individuals taking part in interviews, nor will we report them in findings to be disseminated as part of this project. Given the low number of people in the study and the identification of participants (e.g., stakeholders in the Department of Health) it is possible that their identities could be inferred and we will make this risk clear during the consenting process.
- ii. A secondary risk of participation in this Aim is loss of time from participation in interviews and/or discomfort with the questions asked or nature of the conversations. All participation will be voluntary and participants will be free to pause, interrupt, or not respond to any questions or content areas that make them uncomfortable.

b. Benefits

- i. Most study participants in Aim 1 will derive no direct benefit from participation in the study.
- ii. Some participants might gain a personal sense of pride from knowing they are contributing to development of a system that intends to improve hypertension care in their community, or for the opportunity to contribute to its design.
- iii. If one of the interventions is ultimately successful, this study might provide a benefit to the community by helping to guide development of an improvement system of hypertension care.
- iv. A financial incentive of R50 of airtime (telephonic), R50 in cash (in-person), or a R50 food voucher will be provided to participants for their participation in discussion groups and interviews, subject to COVID-19 restrictions in place.

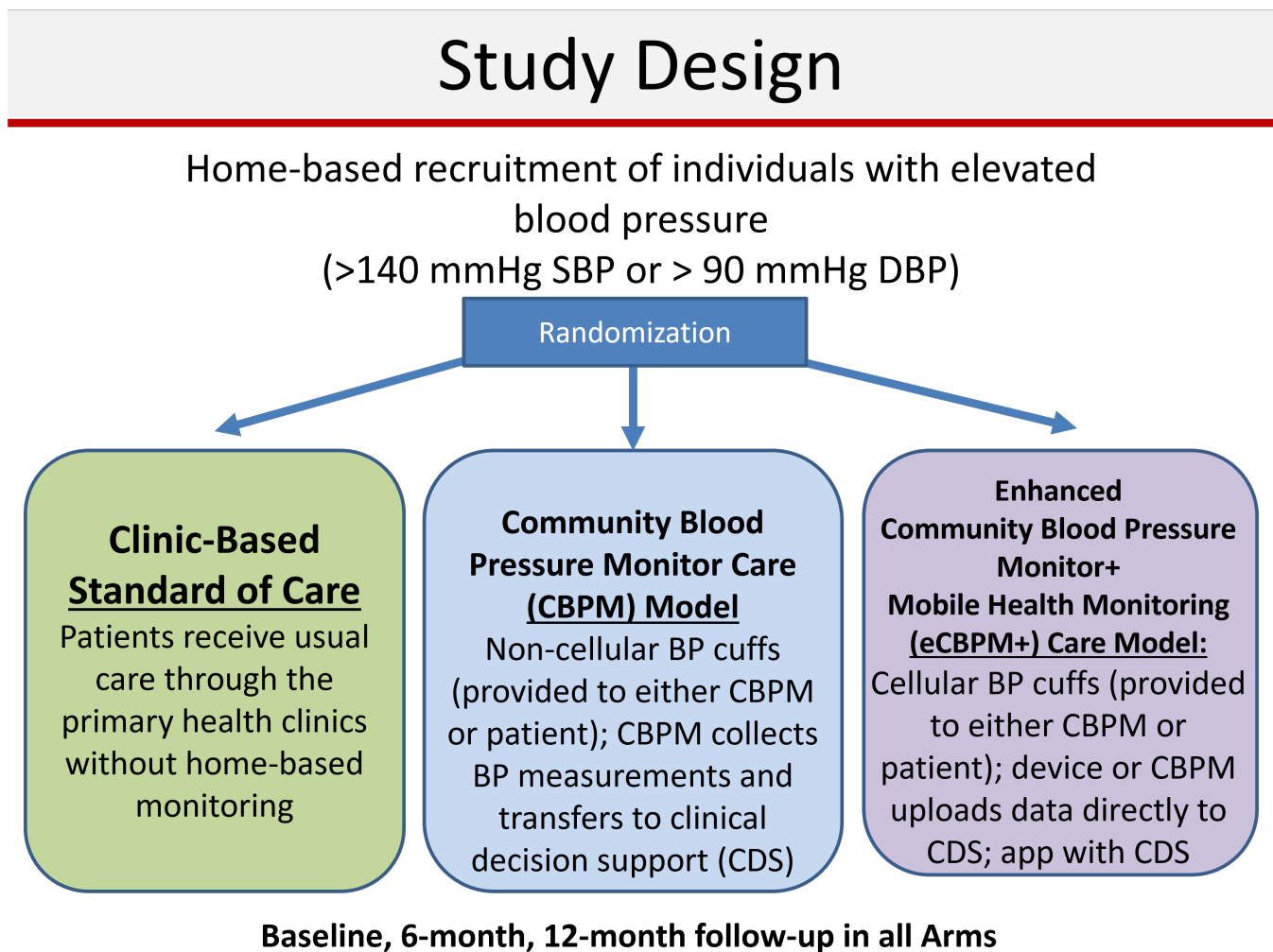
V. AIM 2: IMPLEMENTATION CLINICAL TRIAL

Determine the effectiveness of community-based, technology-supported interventions to reduce systolic blood pressure and increase blood pressure control among individuals with uncontrolled hypertension in rural South Africa.

A. Aim 2 Overview

This is randomized clinical trial intended to identify the optimal strategy of blood pressure management in rural South Africa. Participants will be randomized into one of three arms of hypertension care: 1) clinic-based standard of care model (SOC); 2) community blood pressure monitor-based blood pressure monitoring model (CBPM); 3) an enhanced community blood pressure monitor-based model with mobile health blood pressure monitoring (eCBPM+). (Figure 1). Eligible participants will be recruited from prior community-based hypertension screening programs, CBPM-led hypertension screening activities, and/or from trial clinics where they are accessing care. Consenting participants will be randomized to one of the three study arms. Independent of clinical care, all participants will be seen at enrollment, at 6 months, and at 12 months for BP monitoring and data collection by study nurses for outcome assessments.

Figure 1. Study Schema



The primary effectiveness outcome will be assessed in an intention-to-treat analysis and defined as the change in systolic blood pressure (SBP) 6 months after enrollment. The secondary effectiveness outcome will be the proportion of participants with controlled blood pressure, as defined by an SBP <140 mmHg and a diastolic BP (DBP) <90 mmHg 6 months after enrollment.

B. Eligible Study Population

Residents living in the catchment area of publicly operated rural primary care clinics in the Umkhanyakude District in northern KwaZulu Natal.

C. Eligibility Criteria

a. Inclusion Criteria

- Age greater than 18 years old.
- Residing in uMkhanyakude District in northern KwaZulu-Natal in an area that is served by a CBPM.
- Elevated blood pressure (blood pressure > 140/90 mmHg) on two measurements.

b. Exclusion Criteria

- Pregnant or breast-feeding women.
- Severe, symptomatic hypertension with a measured blood pressure > 180/110 mmHg.
- Known, advanced chronic kidney disease. GFR < 60 ml/min/1.73 m².
- Current use of at least 3 different anti-hypertensive therapies at full dose.
- Planning to move within the next 24 months.

D. Subject Recruitment

a. Participant Identification

We will identify potentially eligible participant from three sources: 1) those presenting to the trial clinics with elevated blood pressure, 2) individuals who are diagnosed with hypertension during home visits by CBPMs, or 3) individuals with elevated blood pressure identifying through screening activities for hypertension conducted in the study catchment area, such as the Vukuzazi Study. Clinic and research staff from these activities will notify study nurses of potentially eligible participants who will then conduct eligibility assessments, either at the clinic, or in the case of notification after a home or community-based screening, at participant homes. Study nurses will describe the study and screening procedures, including the required screening for pregnancy and kidney function to confirm eligibility. Those who agree to be screened will have their eligibility determined by the nurse using a screening questionnaire and measurement of blood pressure. Eligible patients who agree to participate will then be asked to review and sign the informed consent form. The study nurse will answer any questions the patients may have about the study. Once informed consent is obtained, the study nurse will conduct the pregnancy test (if applicable) and a point-of-care creatinine test (Abbott/Piccolo Xpress) to complete the enrollment process. Patients who are not pregnant and have glomerular filtration rate greater than 60 ml/min/1.73 m² will be enrolled in the study. Patients who are pregnant, have abnormal renal function, or are confirmed to have uncontrolled hypertension will be referred to clinic for additional care by the nurse and enrollment will not be completed.

E. Informed Consent

Informed consent procedures will be performed by research nurses who have been trained in the ethical conduct of human subject's research and informed consent procedures. This procedure will be carried out in the participant's in a private area of the home or clinic in either English or in isiZulu. Any eligible patients who previously participated in Aim 1 discussion groups and who are randomly selected for recruitment in the RCT, will be asked to sign the RCT informed consent form if they agree to participate.

F. Randomization

Consenting participants will be randomized by the REDCap randomization module to the standard of care (SOC), (CBPM) or (eCBPM+) study arms (Figure 1). Randomization will be stratified by clinic and active use of anti-hypertensive therapy. Randomization will be conducted in blocks of 9. In brief, after screening has been completed, eligibility confirmed, and informed consent forms signed, a study participant is given a unique consecutive identification number in REDCap. The randomization field is selected, and the research assistant is informed which arm the participant has been selected for by the application. Strategy allocation will be unblinded to participants or clinic staff.

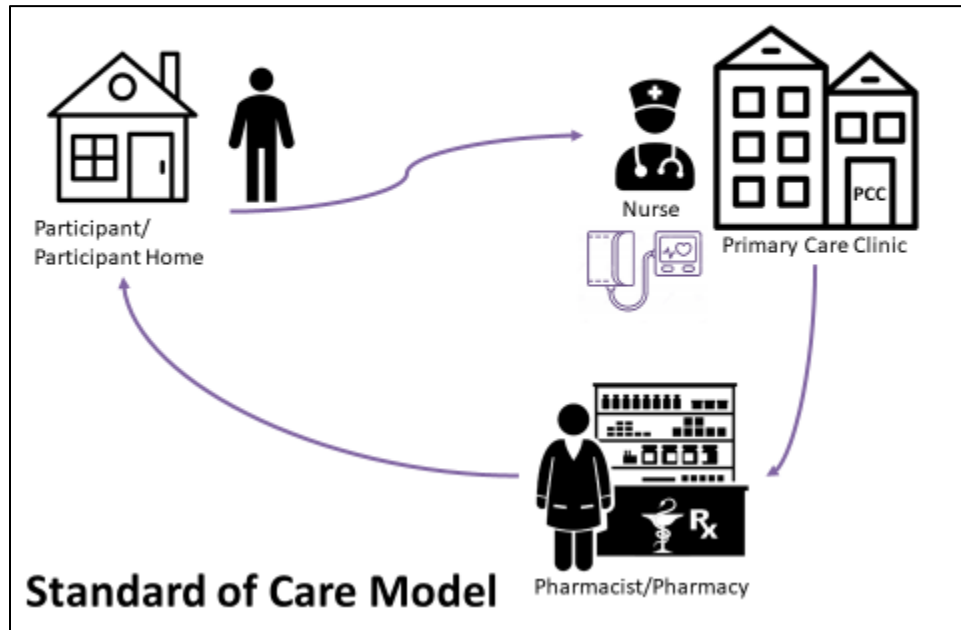
G. Aim 2 Study Procedures

a. Blood Pressure Monitoring Procedures by Study Arm

i. SOC: Baseline Visit for Clinic-Based Standard of Care Participants (Figure 2)

All study participants, including in the SOC arm, will receive standardized educational materials for BP medication adherence support, nutritional guidelines, lifestyle modification techniques for individuals with elevated blood pressure, and medications for individuals with elevated blood pressure. Participants in the SOC arm will be referred to their clinic for initiation (if newly diagnosed) or active care (if previously diagnosed) as per standard clinical protocols. All care will be provided at the clinic. Routine care consists of regular visits to the clinic until BP is under control (<140/90 mmHg) and then at 6 monthly intervals. BP measurements to guide management decisions will be made at the clinic using standard clinic equipment. Symptoms related to hypertension and/or medications will be assessed at each visit. Medications available will include medications on the South African Essential Drug list and which are available in the pharmacy (which include hydrochlorothiazide, enalapril, amlodipine and spironolactone). Prescriptions are picked up at the clinic pharmacy by patients as per routine protocol at the clinics. CBPMs may also conduct monitoring as guided by clinical guidelines and as advised by their clinical supervisors during the study period to assess for adherence and provide education.

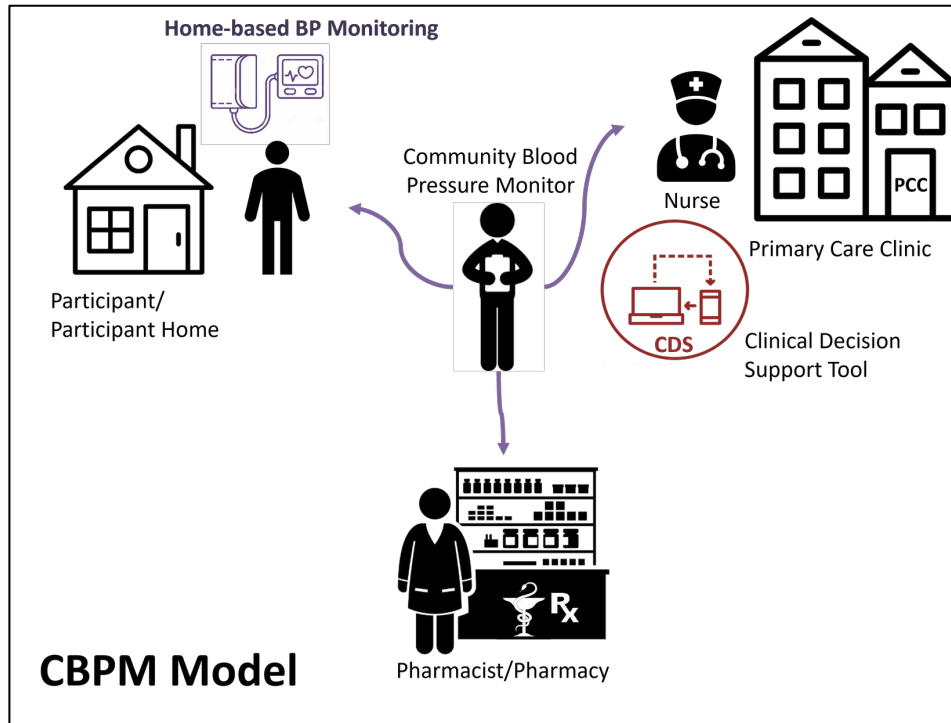
Figure 2. Standard of Care Model.



ii. Intervention 1: Community Blood Pressure Monitor Model (CBPM) (Figure 3)

Participants in the (CBPM) arm will be given an Omron BP Cuff and a standardized training on its operation and assigned a CBPM from the study teams. The participant will be instructed to take daily BP measurements using their BP cuffs. CBPMs will return to participant homes every 2-4 weeks, or as guided by the clinic nurse, to collect BP measurements and enter them into a data collection system, assess for symptoms, and discuss treatment adherence and lifestyle recommendations. BP readings will be transmitted to the assigned nursing supervisors at each clinic, who will initiate and/or tailor medications and other recommendations with guidance from a standardized clinical decision support algorithm, based on SA DoH hypertension control guidelines. Treatment decisions will be made by the nursing supervisors. Participants will either obtain medication(s) at the pharmacy or, as possible, have them delivered by a CBPM. As with the SOC arm, medications used will include those on the South African Essential Drug list, which are available in the clinic pharmacy (including hydrochlorothiazide, enalapril, amlodipine and spironolactone). Participants who achieve optimal blood pressure control may have visits spaced out if recommended by the nursing supervisor.

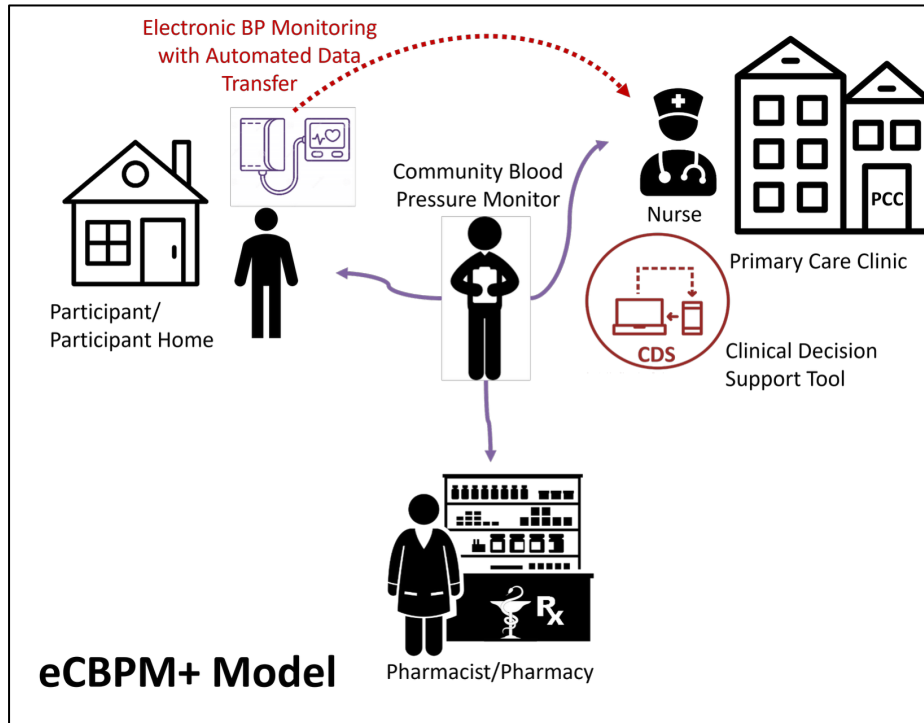
Figure 3. Intervention 1: CBPM Care Model.



iii. Intervention 2: Enhanced Community Blood Pressure Monitor-based with mobile health blood pressure monitoring model (eCBPM+) (Figure 4)

Participants in the (eCBPM+) Arm will also be given a home BP cuff, but in this case these cuffs will include cellular network capability (Blipcare model), such that BP data can be directly transmitted to the electronic platform to allow nursing supervisor review. Similar to the standard CBPM arm, they will also be given training on its operation and assigned a CHW from the study team. Participants in this arm will be instructed to take daily BP measurements, which will be automatically uploaded onto the server to be made available by the nurse supervisors. CBPMs will return to participant homes every 2-4 weeks to ensure functionality of the devices and transmission, collect BP measurements if the system is not functional, assess for symptoms, and discuss treatment adherence and lifestyle recommendations. Nursing supervisors at the clinic will use the remotely collected BP data to initiate and tailor medications guided by the same standardized clinical decision support (CDS) algorithm, based on SA DoH hypertension control guidelines. Treatment decisions will be made by the nursing supervisors. Participants will either obtain medication(s) at the pharmacy or, as possible, have them delivered by a CBPM. As per the SOC arm, medications used will include those on the South African Essential Drug list and which are available in the clinic pharmacy (include hydrochlorothiazide, enalapril, amlodipine and atenolol). Participants who achieve optimal blood pressure control may have visits spaced out if recommended by the nursing supervisor.

Figure 4. Intervention 2: eCBPM+ Care Model.



b. Study Visit Schedule

i. **Visit 1: Enrollment**

At Study Visit 1, participants will complete the baseline questionnaire to collect sociodemographic, clinical and treatment history, self-reported medication adherence, quality of life, and resource allocation data (Table 1). Enrollment BP measurements will be collected by study nurses (independently from the CHW program) using standard BP measuring devices (OMRON model). Three measurements will be taken from the seated position with five minutes between each measure [14]. As described during the recruitment phase, all participants will receive a point of care (POC) creatinine (Abbott/Piccolo Xpress) to determine both eligibility and to guide BP regimen selection. Study staff will also review participant clinic records to collect data on clinic treatment history and blood pressure measurements in the past.

ii. **Visit 2: 6-month BP Measurement Assessment and Medication Use**

A follow-up visit will be conducted by study staff in all three arms approximately 6 months after enrollment (allowing for a one-month window). BP measurements will be conducted by study nurses independently from the CHW program using standardized Omron BP cuffs. Three measurements will be taken from the seated position with five minutes between each measure [14]. At the 6-month visit we will additionally collect data on medication regimen changes and adherence (Table 1).

iii. **Visit 3: 12-month BP Measurement Assessment and Evaluation of BP Device Function**

A final home-based study visit in all three arms will be conducted 12 months after enrollment (allowing for a one-month window period). BP measurements will be conducted using standardized Omron BP cuffs by study staff, independently of CHW

interactions with study participants. Three measurements will be taken from the seated position with five minutes between each measure [14]. We will also collect data on self-reported medication regimen changes, adherence, quality of life, and resource use (Table 1).

iv. Extension phase and additional study visits: 18 and 24-month BP Measurement Assessment and Evaluation of BP Device Function

At the conclusion of the 12-month study visit, individuals in the community-based blood pressure arms will be invited to consent for a continuation phase of the project to assess the longer-term impacts of the project. The extension phase will coincide with the period when initial participants complete their 12-month visit to the conclusion of all participants completing 12 month visits. Participants who agree to this continuation will remain in the community-based program, retain their BP cuffs, and be visited by CBPMs with their blood pressure treatment monitored by clinic nurses. For those who consent to the extension phase, study team members will continue home-based visits every 6 months to monitor blood pressure readings and complete questionnaires for study purposes.

v. Missing and Late Appointments

If study participants are not present for study visits, study staff will attempt to call them to encourage another time for study visit. For participants who do not return calls within 7 days of a scheduled visit and are unreachable by phone, a study staff member will attempt to track them using a standardized lost-to-follow-up form and procedures. If participants are located, study staff will study complete measures and encourage them to allow for a follow-up home visit to complete procedures if the participant agrees.

Table 1. Summary of Study Visit Procedures

	Enrollment Visit	6-Month Visit	12-month Visit	18-month Visit	24-month Visit
Screening and eligibility form	<input type="checkbox"/>				
Consent form	<input type="checkbox"/>				
Point of care creatinine	<input type="checkbox"/>				
Sociodemographic questionnaire	<input type="checkbox"/>				
Tracking form	<input type="checkbox"/>				
Hypertension KAP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Medication adherence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hypertension treatment history	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Resource use form	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Health related quality of life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Blood pressure measurements	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chart review for medication and laboratory history	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

H. Data Systems and Management

a. Data Systems

i. REDCap Study Database

Study data will be directly entered into a study [REDCapDatabase](#). REDCap is a password protected, online database application that allows for storage of study data on encrypted servers in the United States. The application includes features for field limits,

data quality control, study scheduling, randomization, and real-time study monitoring. Questionnaires and clinical records will be completed in real-time and entered by study staff using encrypted study mobile tablets. The REDCap application allows for both online (real-time) data entry or, when internet service is not available, offline entry with syncing to the server when internet becomes available again.

ii. Hypertension Management Application

In both intervention arms, we will use a clinical decision support system (CDSS). The clinical decision support will receive blood pressure measurements information every two to four weeks (either manually by the CBPM/Nurse team in Intervention (CBPM) or via direct cellular data transfer in Intervention (eCBPM+)). The CDSS will be designed to make treatment recommendations based on the participants blood pressure measurements, prior drug reaction history if any, and current treatment status in accordance with the South African Hypertension guidelines in use in the PCCs in KZN. Additionally, if any laboratory tests are recommended based on the guidelines, the CDSS will also recommend these tests be done.

b. Data Protection and Confidentiality

Paper forms that include participant protected health information will be stored on the day of enrollment in participant specific folders within locked file cabinets in locked research offices. Only study staff will have access to the file cabinets. All other study data will be free of identifying information. Data will be stored on an encrypted data servers hosted by the Africa Health Research Institute. Access to the study database both on site and remotely is restricted to study staff and password protected. All study mobile tablets will be password protected and encrypted prior to study initiation. Data collected on mobile tablets will be uploaded to the server in real-time during data entry or synced to the server as soon as data/Internet access becomes available if it is not during data entry, using the REDCap Offline Application. Data shared between tablets and the server will be encrypted during transmission. Any data shared with the clinical decision app that will be used to generate treatment recommendations for the nurse to use in managing hypertension will also be encrypted during transmission. No personally identifiable information will be shared with, or stored by, the clinical decision application, in compliance with the South African Protection of Personal Information Act (POPI) regulations.

c. Data Sharing

During study conduct, data access will be restricted to study. Upon completion of the study, in compliance with guidance by the study funders (U.S. National Institutes of Health), study data will be fully de-identified and posted to a public data repository where it may be shared with other scientists for secondary use.

d. Specimen Collection and Testing

A single blood specimen will be collected in this study at enrollment for renal function assessment to determine eligibility and help guide therapy. Participants will receive a point-of-care creatinine (Cr) using a lancet for finger-stick blood collection to evaluate renal function which can be used for study eligibility and initiation of certain therapies depending on normal renal function. No additional blood or specimens will be collected as part of the trial.

e. Data Monitoring and Quality Control

Study data coordinators will perform routine reviews of data quality to identify unusual values and missing data entries. Initial analyses will include common exploratory data analyses, table construction, and scatterplots to assist in data quality control, randomization balance, and exploring for possible outliers. A data flow map will be developed to describe the process for data flow from the home to the nurses and the CDSS and back to the CBPMs and then back to the participant's home in repeating cycles in Intervention (CBPM) and (eCBPM+). Additional checks will be in place for data coordinators to assess face validity of key indicators such as blood pressure measurements and medication prescriptions.

I. Study Monitoring and Regulatory Oversight

a. Staff Training

i. Research Staff

All research assistants will complete training through the CITI biomedical human subjects research course, a South Africa-based good clinical practice course, and/or a refresher course, as indicated. Only research staff fluent in the local languages (IsiZulu) will conduct informed consent and survey procedures. Study staff certified in phlebotomy will complete any blood collection procedures. Study staff will maintain active research ethics certification and attend any annual research ethics conferences as mandated by local policy at their institutions.

ii. Provider Staff

Prior to study initiation, nurses will complete a training to use the CDS and its treatment recommendations to manage hypertension using the current guidelines. CBPMs will be trained to understand hypertension as a condition, how to measure blood pressure using automated cuffs, retrieving recorded blood pressure measurements from the cuff memory, and educating patients about managing blood pressure symptoms and the importance of proper use of medication. The course will be designed and directed by study Co-Investigators Drs. Thomas Gaziano, Shafika Abrahams-Gessel and Nambulelo Magula and conducted at the study sites.

b. Regulatory Oversight and Safety Monitoring

Study protocols will be submitted for review to the University of KwaZulu-Natal Biomedical Research Ethics Committee and the Institutional Review Board of Massachusetts General Brigham. The protocol will also be submitted for registration at Clinicaltrials.gov. All protocol amendments, adverse events, unexpected events, and data monitoring review activities will also be submitted to each of these regulatory authorities per the guidelines.

i. Safety Monitoring:

The study co-principal investigators will be ultimately responsible for study conduct, safety, reporting, and interactions with regulatory authorities. Study PIs will ensure: 1) proper conduct of the informed consent process (e.g. that informed consent is obtained before proceeding with study procedures); 2) goal enrollment of study subjects; 3) adequate and high-quality collection and analysis of data; 4) the implementation of study procedures in accordance with study standard operating procedures in order to ensure monitoring of subjects for possible adverse events; 5) prompt review and

response to adverse and unexpected events, and reporting to IRBs; and 6) maintenance of the privacy and confidentiality of study subjects. The PIs will be in contact with the research team on a regular basis to review the progress of the study and address any human subject issues that occur. These discussions may involve adverse event prevention measures, recruiting of appropriate study subjects, research staff training on protection of human subjects, as well as occurrence of adverse events, unexpected incidents, or protocol problems.

In compliance with National Institutes of Health policies, we will establish a formal Data and Safety Monitoring Board (DSMB) for study safety monitoring. The DSMB will meet after completion of the 6-month visit of 50% of study participants to conduct an unblinded assessment of study safety outcomes by arm, including adverse events and severe adverse events and present a formal letter to the study investigative team on recommendations to continue the study. The DSMB will be comprised of three clinical experts in epidemiology and/or hypertension care and will be guided by a DSMB charter signed by all members. Study data will be summarized by the study statisticians who will join the DSMB meetings as non-voting members.

Finally, the study statistician and co-investigators will meet annually to perform the following activities: a) review the research protocol and plans for data and safety monitoring; b) review progress of the trial, including analysis of data quality and timeliness; subject recruitment, randomization and retention; subject risk versus benefit; and other factors that may affect outcome. c) review serious and unexpected adverse event reports, provide commentary, and provide oversight to ensure that reports are relayed to individual IRBs; d) review proposed modifications to the study prior to their implementation.

ii. Adverse and Unexpected Event Reporting:

To identify adverse events: (1) study staff will perform a clinical review at each study visit and (2) study staff will instruct participants to report any unexpected or severe adverse events to their assigned research assistant. Such a report will immediately be brought to the attention of study principal investigators. Any adverse events that are unanticipated (i.e., not related to standard HTN clinical care or thought to be directly related to study procedures) or severe (e.g. death) will be recorded on an adverse events log form and brought to the attention of the principal Investigator, as well as be reported to participating ethical review committees within 7 days. The relevant committee will determine whether it is appropriate to pause the study or alter the study protocol and will provide suggestions/modifications to the study procedures as necessary. Possible modifications include adding adverse events to the consent form and re-consenting all study participants. The site principal investigator will be responsible for monitoring participant safety at each site on a monthly basis at regularly scheduled research meetings. They will keep a written log of all events and ensure that the ethical review committee is contacted when necessary. They will also keep a log of the outcome of committee decisions regarding adverse events and apprise the research team of any changes that need to occur as a result of such decisions.

J. Statistical Considerations and Analyses

a. Sample Size

Based on prior studies we anticipate a mean blood pressure of 150/95 mmHg among

randomized participants with a standard deviation of 19 mmHg [5]. To detect a 5 mmHg difference between arms in the change of blood pressure from baseline to 6 months, we will need to enroll 774 participants (258 per arm) to provide 80% power, assuming 20% loss to follow-up, a correlation between baseline and follow-up measurements of 0.5, and an alpha of 2.5% to account for multiple testing with comparison between the SOC and both intervention arms (Table 2). This same sample size will also give us greater than 80% power to detect an increase in the proportion of participants who achieve BP control (defined by a systolic BP <140 mmHg and diastolic BP <90mm Hg) at 6 months from 30% in the SOC arm to 45% in the interventions arms, or from 40% in the SOC to 56% in the intervention, also allowing for an alpha of 2.5% to account for multiple testing. We estimate that there are over 2,500 individuals to draw this sample from within our catchment area served by the three most heavily population primary care clinics in the catchment area (Table 3).

Table 2. Differences in change from baseline that can be detected with 80% power

330	264	5.0	19.0	0.20	80%
258	206	5.0	19.0	0.50	80%
148	118	7.5	19.0	0.20	80%
115	92	7.5	19.0	0.50	80%

Table 3. Hypertension visits and patients at clinics in the study catchment area (2020)

Clinic	Hypertension Visits	Patients with Hypertension	Patients with Uncontrolled Hypertension
Esiyembeni	458	152	163
Gunjaneni	1481	424	245
Hluhluwe	1010	406	828
KwaMsane	1997	768	168
Machibini	1692	428	7
Madwaleni	814	406	507
Mpukunyoni	1277	569	63
Mtubatuba	1089	545	36
Nkundusi	1392	465	578
Ntondweni	869	288	163
Somkhele	1685	652	245
Totals	13764	5103	2595

K. Study Outcomes

- a. Primary Outcome of Clinical Trial: Difference between arms in change from baseline in systolic blood pressure (SBP) 6 months after enrollment.
- b. Secondary Outcomes:
 - Proportion with blood pressure control at 6 after enrollment (<140/90 mmHg).
- c. Safety Measures:
 - Number of adverse drug reactions.
 - Proportion of participations retained in hypertension care at 6 months.

L. Aim 2 Analysis Plan

We will summarize participant sociodemographic and clinical characteristics at baseline in all three arms. We will use linear regression to estimate the difference between arms, and its 95% confidence interval (CI), in systolic blood pressure at 6 months, adjusted for baseline systolic BP. We will use logistic regression to estimate odds ratios (OR) and 95% CIs for the impact of the intervention on the proportion of participants who achieve blood pressure control (<140/90) at 6 months.

Characteristics of individuals who are lost to follow-up will be tabulated by study arm. Since study nurses will visit all participants at home to measure blood pressure at 6 and 12 months, we do not expect there to be differential loss to follow-up between arms. In the primary analyses, participants with missing data at 6 months will be excluded. In sensitivity analyses, those with missing measurements will be considered to have no change in systolic BP and uncontrolled BP. Missing values may also be imputed using multiple imputation.

In pre-planned secondary analyses, we will fit regression models stratified by sex (to assess for sex as a biologic variable), age strata, socioeconomic status and baseline co-morbidities (i.e. obesity and HIV) to determine sub-group effect sizes and test the significance of an interaction term between sub-groups and the intervention to assess for effect modification.

A detailed statistical analysis plan will be prepared before the data are examined by treatment arm.

M. Risks, Protection from Risks and Benefits to Study Participation in Aim 2

a. Risks and Protections

One risk to participation is breach of confidentiality. Study staff will be trained in confidentiality and all staff members will be required to sign confidentiality agreements. Assurance of privacy in testing and communication of results will be done. Quality assurance processes will include regular support/supervision visits in the field and self-evaluations in this study. To ensure confidentiality of participants, all data will be coded by subject number. Data recorded on paper will be kept in locked cabinets with access only by members of the research team. There will be strict limited access to electronically stored data as well, using password protection. Research records will be kept confidential following national regulations. The subject's name or other personal identifiers will not be included with specimens sent to the laboratory, which will be identified only by a code number. Interviewers and support staff will be trained on procedures for maintaining confidentiality.

We will conduct a single specimen collection during this study to conduct point of care creatinine testing that will be administered by trained study staff. A trained nurse will collect blood from a pin prick using standard precautions requiring a few drops of blood (< 1ml) to be drawn.

Study participants in both the SOC and intervention arms with uncontrolled hypertension will receive one of four blood pressure medications on the South African Essential Medication list according to the local guidelines including: hydrochlorothiazide, enalapril or other angiotensin converting enzyme inhibitor, amlodipine, or a beta-blocker. No experimental medications will be used. Participants will be followed for side-effects in accordance with the South African hypertension guidelines by the nurses and the CBPMs. All participants who experience any adverse event will receive follow-up until adverse event is resolved by the local study staff. Severe and serious adverse events will

be documented and reported to the involved regulatory bodies per their regulations. A secondary risk of participation in this Aim is loss of time from participation in interviews and/or discomfort with the questions asked or nature of the conversations. All participation will be voluntary and participants will be free to pause, interrupt, or not respond to any questions or content areas that make them uncomfortable.

Participants in the CBPM and eCBPM+ arms of the study have a risk of receiving less than the standard of care by not attending the clinic, particularly if data from the home blood pressure cuffs are not being transmitted manually or automatically to the clinical decision support system. Protections will be in place such that the nurses who remain the backbone of hypertension care in all intervention and control clinics will have the ability to communicate with the CBPM to ensure a) blood pressure data is transmitted properly or faulty equipment is repaired or replaced, b) prescriptions are available for patients or delivered as allowed, or c) communicate through the CBPMs so that the participant can come in for a visit or make a home visit to ensure that care consistent with guidelines is available to all participants.

b. Benefits

Participants may lead to a reduction in their blood press level and overall improved blood pressure control. Participants in the intervention arm may develop proficiency in managing their own blood pressure and learning about the operation of a home blood pressure device.

Participants may gain a better understanding of their cardiovascular risk profile. Any identified with having advanced renal disease may be referred for additional care and therapy.

Some participants might gain a personal sense of pride from knowing they are contributing to development of a system that intends to improve hypertension care in their community, or for the opportunity to contribute to its design.

If one of the interventions is ultimately successful, this study might provide a benefit to the community by helping to guide development of an improvement system of hypertension care.

A financial incentive of R450 will be paid to participants for participation in the clinical trial. An incentive of R150 will be given after each study visit at baseline, month 6 and month 12. These incentives are consistent with current SAHPRA recommendations.

VI. AIM 3

Determine the fidelity, sustainability, acceptability, and cost-effectiveness of community-based, technology-supported hypertension interventions to reduce blood pressure in rural KwaZulu-Natal.

Aim 3 will have two primary components:

(3a) Building on the qualitative research conducted before and early in the trial, we will conduct additional qualitative research to assess the acceptability of the interventions and quantitative monitoring of implementation throughout the trial to assess fidelity and sustainability.

(3b) We will record the costs of care and of the interventions and determine the cost-effectiveness of the intervention with microsimulation model (CVD PREDICT) that uses individual-level risk factor data and health cost inputs.

A. Methods

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

The use of the CMIR and TFA (Aim 1) will be extended to evaluate the overall acceptability, fidelity, and sustainability of the intervention.

Approximately 12 months after the start of the trial we will conduct key informants interviews and individual interviews with health workers and trial participants. Where appropriate we will include the same individuals sampled for Aim 1, to compare their experiences during the trial with their initial expectations and preferences. Qualitative data collection and analysis will be similar to Aim 1 methods, adapted as necessary to accommodate unforeseen issues that arise during the trial.

Study documentation (e.g. coordination meeting minutes, supervision visit reports) will be reviewed to extract any relevant information contributing to document adaptations to implementation, and thereby fidelity, decision-making process and thereby acceptability (and feasibility), and short-term sustainability.

These qualitative data will be complemented by collection of quantitative indicators of fidelity and sustainability of implementation. An assessment of the intervention's fidelity will be performed 6 and 12 months after study enrollment (based on monthly data collection), while sustainability will be measured at the 12-month, 18-month, and 24-month visits. Data will be collected through repeated completion of intervention fidelity clinic checklists to estimate adherence, exposure, and quality of the intervention.

b. (Aim 3b) Cost-effectiveness

Cost-effectiveness of the intervention compared to standard of care in blood pressure management, will be calculated as incremental costs for absolute changes in blood pressure (costs/mmHg) and incremental costs per extra participant with controlled blood pressure. The Harvard CVD PREDICT microsimulation model for cost-effectiveness and changes in CVD-related health outcomes will be used to conduct this analysis. The cost-effectiveness will be calculated across the entire intervention, as well as separately by each of the study arms.

B. Study Outcomes

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

Study outcomes measuring acceptability, fidelity, and sustainability of the intervention are summarized below in **Table 4**.

c. (Aim 3b) Cost-effectiveness

- Costs to participants of health care including (where applicable) the interventions
- SBP reduction and blood pressure control resulting from the interventions
- Quality adjusted life years (QALYs)
- Incremental cost-effectiveness ratios (ICERs), that is, incremental cost per mmHg SBP reduction, per extra participant with controlled blood pressure, and per QALY gained as effects of the interventions

Table 4. Summary of acceptability, fidelity, and sustainability outcome measures for Aim 3a

Category	Study Outcomes	Source/Measurement
Acceptability	- Participant and provider perception of the intervention and clinical decision support tools.	- Key informants interviews. - Individual interviews.
Fidelity	- Proportion of successful and failed BP data transmission events, among all transmitted BP data events.	
	- Proportion of CDS-recommended treatment changes initiated by nurse/CBPM, among all CDS-recommended treatment changes.	
	- Number of BP cuffs distributed to participants in 2 intervention arms.	- Study check lists.
	- Number of BP readings manually recorded by intervention participants.	- CDS records.
	- Number of CBPMs trained on HBPM and data tool input/management.	- Study check lists.
Sustainability	- Number of participants with treatment initiation during study period.	- Participant study records. - Outreach team leader supervision records.
	- Number of BP cuff training sessions provided to participants at home by CBPMs.	- CBPM study records.
	- Number/frequency of CBPM home visits conducted versus planned	- CBPM study records
	- Number of participants counseled in lifestyle modification and medication adherence at home by CBPMs.	- CBPM study records.
	- Number of clinics adopting use and distribution of BP cuffs for HBPM.	- Study check lists.
	- Proportion of clinics sustaining use and distribution of BP cuffs for HBPM at 12 months, among those who distributed BP cuffs at the start of the study.	- Study check lists.
	- Proportion of participants retained in hypertension care at 12 months, among enrolled study participants.	- Participant study records.
Sustainability	- Absolute change in systolic blood pressure (SBP) between 6 and 12 months after enrollment, among enrolled study participants.	- CDS records
	- Proportion of participants retained in hypertension care at 12 months, among enrolled study participants.	- Participant study records.
	- Absolute change in systolic blood pressure (SBP) between 6 and 12 months after enrollment, among all study participants.	- CDS records.

C. Data Sources

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

Both the fidelity and the sustainability of the intervention will be assessed using data obtained through review of study check lists, the participant study records (including prescriptions), CDS records, CBPM study records, outreach team leader supervision records, and coordination meeting minutes.

Key informant and individual interviews will assess overall acceptability and experience of the intervention.

b. (Aim 3b) Cost-effectiveness

Cost data will be obtained from trial participant interviews, KZN DoH unit prices, and analysis of intervention delivery.

The trial will provide individual level outcome data on SBP and blood pressure control 6 and 12 months. The PREDICT model will use these data to predict long term effects of the interventions on quality adjusted life years (QALYs)

D. Recruitment

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

As appropriate, for key informants and individual interviews, we will try to recruit from the same sample used in Aim 1 in order obtain maximal information about changes in expectations and experiences before and after the trial. Key informants will be identified and contacted by study investigators at AHRI from current and prior collaborators working on improving health care in this rural population. Health care workers will be identified from personnel records at the study clinics and be invited to participate in interviews by study investigators. Participants will be identified from clinic registers for hypertensive patients.

b. (Aim 3b) Cost-effectiveness

Participants will not be enrolled for this part of Aim 3 and cost data will be obtained as described in Section C(b) above.

E. Enrollment

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

i. Inclusion Criteria for Key Informants

- age 18 and over.
- representative of the KZN DoH for involved in management of primary care delivery programs.

ii. Inclusion Criteria for Health Care Workers

- age 18 and over.
- currently employed as a health care worker (physician, nurse, CHW, pharmacist, clinic administrator/operational manager) at one of the study clinics.

iii. Inclusion Criteria for Participants

- age 18 and over.
- diagnosed with uncontrolled hypertension.
- selection based on pre-defined criteria such as age, gender, trial arm, patients accepting/refusing the intervention.

- b. (Aim 3b) Cost-effectiveness
Not applicable

F. Sample Size

- a. (Aim 3a) Fidelity, Sustainability, and Acceptability
- Key informants interviews: minimum 5
 - Interviews with professional health care workers: minimum 15 (3 per facility), including chronic nurse, OM, nurse “supervising” CHW, doctors (supervisory role)
 - Interviews with CHW (minimum 3 per clinic)
 - Interviews with patients: minimum 15
- b. (Aim 3b) Cost-effectiveness
All trial participants will be included in analysis of costs and cost effectiveness.

G. Informed Consent

- a. (Aim 3a) Fidelity, Sustainability, and Acceptability
As in Aim 1, key informant discussants will be invited to participate in discussions about the planned study and their participation in meetings will be taken as consent to participate.
Study research assistants will recruit participants enrolled in the study and health care workers to participate in the focus groups.

Persons who participated in Aim 1 activities and who will participate in Aim 3 activities, will be reconsented regardless of whether they provided verbal or written consent in Aim 1. Consenting procedures for Aim 3 will be identical to those described in Aim 1.

- b. (Aim 3b) Cost-effectiveness
This will be included in the consent to participate in the trial.

H. Data Collection

- a. (Aim 3a) Fidelity, Sustainability, and Acceptability
Data on fidelity outcomes will be obtained from study checklists and data collected with the electronic hypertension management tool in the intervention arms at 6,12, 18 and 24 months. Sustainability measures, including changes in systolic blood pressure, will be collected using the same sources at 12 months in the intervention arms. In the standard of care arm changes in systolic blood pressure at 12 months and medication use will be obtained through participant chart reviews. All data will be combined into a database for analyses and all personal identifiers will be removed prior to analysis. Interviewers will use guides with open-ended questions to collect qualitative data on the overall acceptability of the intervention.
- b. (Aim 3b) Cost-effectiveness
Resource allocation assessments in all three study arms will be conducted at 6 and 12 months after the start of the trial using a time and motion study over five clinic days, along with medical records reviews and participant exit interviews. Using these measurements, the public-sector unit costs for managing hypertension will be calculated, including human resources, diagnostics and supplies, therapeutics, and home blood pressure monitors. Costs will be collected from relevant sources, including clinic sites, the South African

Department of Health, and published reports. A societal perspective will be applied to data collection and analysis.

I. Analysis

a. (Aim 3a) Fidelity, Sustainability, and Acceptability

Quantitative data will be analyzed using Stata Statistical Software (Release 17. College Station, TX) and statistics for fidelity and sustainability outcomes will be generated. Qualitative data analysis will be performed using similar methods as in Aim 1. The key informants and individual interviews will be collected in isiZulu, then transcribed, and translated in English by a team of social science research assistants. A data-led coding framework will be developed, based on themes, which emerge from the data. The research assistants involved in collecting the data will work with other social science team members to agree on the coding framework and performing coding of the data. Thematic summaries will be prepared using the data and a process of building consensus among the whole study team. These summaries will form the building blocks for reporting the findings. Organization of data on the acceptability of the intervention will again be organized into component constructs using the Theoretical Framework for Acceptability, as described in Aim 1.

b. (3b) Cost and Cost-effectiveness

Cost-effectiveness of the intervention compared to standard of care in blood pressure management, will be calculated as incremental costs for absolute differences in blood pressure (costs/mmHg) and incremental costs per extra participant with controlled blood pressure. This analysis will be performed using the Harvard CVD PREDICT model [15] for cost-effectiveness and changes in CVD-related health outcomes. The model will be used to assess the cost-effectiveness of the intervention and to model the impact on the observed change in systolic blood pressure on future CVD events. We will also use the model to translate the intervention effectiveness established during the trial into quality adjusted life years (QALY) and applying assumptions about effects of SBP reductions on survival, quality of life, and complications, based on the extant literature and confirmed locally as part of this trial.

The cost-effectiveness will be calculated across the entire intervention, as well as separately by each of the study arms and expressed in incremental cost-effectiveness ratios (ICERs) and quality adjusted life years (QALYs).

If there is a significant reduction in SBP, we will measure the long term expected reductions in major cardiovascular events and mortality in the population beyond the study period, and for a nationally scaled population. For these predictive cost-effectiveness analyses, we will assess the costs and cost-effectiveness of the intervention modeling the impact on the change in SBP on future CVD events.

Health-related quality of life is measured using the time trade off approach for a reference population in sub-Saharan Africa as adopted in similar cost-effectiveness analyses. We will conduct probabilistic sensitivity analysis by defining probability distributions of variables in the model used to calculate the costs and effectiveness.

We will develop the cost-utility model using best practices outlined by the ISPOR Good Research Practice Task Force [16-19] and guidelines set out by the US Second Panel on

Cost-Effectiveness in Health and Medicine.

J. Risks, Protection from Risks and Benefits to Study Participation in Aim 3a and 3b

a. Risks and Protections

- i. The primary risk to participation is breach of confidentiality. We will not record names of any individuals taking part in interviews, nor will we report them in findings to be disseminated as part of this project. Given the low number of people in the study and the identification of participants (e.g., stakeholders in the Department of Health) it is possible that their identities could be inferred and we will make this risk clear during the consenting process.
- ii. A secondary risk of participation in this aim is loss of time from participation in interviews and/or discomfort with the questions asked or nature of the conversations. All participation will be voluntary and participants will be free to pause, interrupt, or not respond to any questions or content areas that make them uncomfortable.

b. Benefits

- i. Most study participants in Aim 3 will derive no direct benefit from participation in the study.
- ii. Some participants might gain a personal sense of pride from knowing they are contributing to development of a system that intends to improve hypertension care in their community, or for the opportunity to contribute to its design.
- iii. If one of the interventions is ultimately successful, this study might provide a benefit to the community by helping to guide development of an improvement system of hypertension care.
- iv. The cost-effectiveness analysis will provide insight for policy makers into whether the proposed interventions is a good use of health care resources for reducing the disease burden of uncontrolled hypertension substantially in the new community based primary care model.
- v. A financial incentive of R50 of airtime (telephonic), R50 in cash (in-person), or a R50 food voucher will be provided to participants for their participation in discussion groups and interviews, subject to COVID-19 restrictions in place.

VIII. REFERENCES

1. O'Donnell, MJ, Chin, SL, Rangarajan, S, *et al.* Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet.* 2016;388(10046):761-75.
2. Nojilana, B, Bradshaw, D, Pillay-Van Wyk, V, *et al.* Emerging trends in non-communicable disease mortality in South Africa, 1997 - 2010. *S Afr Med J.* 2016;106(5):58.
3. Lim, SS, Vos, T, Flaxman, AD, *et al.* A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2224-60.
4. Mills, KT, Bundy, JD, Kelly, TN, *et al.* Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation.* 2016;134(6):441-50.
5. Wong, EB, Olivier, S, Gunda, R, *et al.* Convergence of infectious and non-communicable disease epidemics in rural South Africa: a cross-sectional, population-based multimorbidity study. *Lancet Glob Health.* 2021;9(7):e967-e76.
6. South African National Department of Public Health. Strategic Plan 2020/21-2024/25 (RP: 108/2020) Available at: <http://www.hsrc.ac.za/uploads/pageContent/3893/NCDs%20STRAT%20PLAN%20%20CONTENT%208%20april%20proof.pdf>. 2019.
7. KwaZulu-Natal Department of Public Health. STRATEGIC PLAN 2020/21 – 2024/25. Available at: <https://www.kznhealth.gov.za/Strategic-plan-2020-2025.pdf>. 2019.
8. Iwuji, CC, Orne-Gliemann, J, Larmarange, J, *et al.* Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial. *Lancet HIV.* 2017.
9. World Health Organization (Who). Community-based health care, including outreach and campaigns, in the context of the COVID-19 pandemic: interim guidance, May 2020. World Health Organization; 2020.
10. South African National Department of Public Health. Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013-17 Available at: <http://www.hsrc.ac.za/uploads/pageContent/3893/NCDs%20STRAT%20PLAN%20%20CONTENT%208%20april%20proof.pdf>. 2013.
11. Proctor, E, Silmere, H, Raghavan, R, *et al.* Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health.* 2011;38(2):65-76.
12. Sekhon, M, Cartwright, M, Francis, JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Services Research.* 2017;17(1):88.
13. O'mara-Eves, A, Brunton, G, Oliver, S, *et al.* The effectiveness of community engagement in public health interventions for disadvantaged groups: a meta-analysis. *BMC Public Health.* 2015;15(1):129.
14. World Health Organization (Who). WHO STEPS surveillance manual: the WHO STEPwise approach to chronic disease risk factor surveillance. World Health Organization; 2005. Report No.: 9241593830.
15. Pandya, A, Sy, S, Cho, S, *et al.* Validation of a Cardiovascular Disease Policy Micro-Simulation Model using Both Survival and Receiver Operating Characteristic Curves. *Med Decis Making.* 2017:272989x17706081.
16. Briggs, AH, Weinstein, MC, Fenwick, EA, *et al.* Model parameter estimation and uncertainty: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. *Value in Health.* 2012;15(6):835-42.

17. Caro, JJ, Briggs, AH, Siebert, U, *et al.* Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1. *Value Health.* 2012;15(6):796-803.
18. Mauskopf, JA, Sullivan, SD, Annemans, L, *et al.* Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. *Value Health.* 2007;10(5):336-47.
19. Neumann, PJ, Sanders, GD, Russell, LB, *et al.* *Cost-effectiveness in health and medicine.* Oxford University Press; 2016.

Summary of Research Protocol Changes

Initial Protocol Date: November 1, 2021

Final Protocol Date: February 15, 2024

Pre-trial protocol changes

- June 25, 2022: Inclusion criteria expanded to restrict enrollment to residents living in an area served by a community health worker.
- June 25, 2022: Screening procedures updated to ensure persons who declined a pregnancy test or point-of-care creatinine test would not be enrolled.
- June 25, 2022: Clarified that individuals who completed Aim 1 patient focus groups would be allowed enrolled if they met criteria for the clinical trial
- June 25, 2022: Financial incentives updated to be R150 per specified study follow-up home visits (R450 for completion of all three study visits) to align with South Africa Health Products Regulatory Authority
- August 15, 2022: The trial was registered on ClinicalTrials.gov, as required by the NIH (NCT05492955).
- November 13, 2022: The trial was registered in the South African National Clinical Trial Registry, as required by the National Department of Health (DOH-27-112022-4895).

Intra- and post-trial protocol changes





- January 18, 2023: At the request of the funder, the protocol was updated to add a data safety and monitoring board (DSMB) to the previously planned data safety and monitoring plan, to conduct an independent safety review after 50% of enrollment was complete.
- January 18, 2023: The term community health worker (CHW) was replaced with community blood pressure monitor (CBPM) in the protocol and in the participant informed consent form for the clinical trial (Aim 2), as recommended by the local department of health.
- January 18, 2023: The participant informed consent forms were updated to reflect South African requirements around protection of personal information (South African POPI Act).
- May 29, 2024: After consultation with the Department of Health, a prolonged extension stage was offered to participants in the intervention arms after the 12-month study completion visit. This allowed them to consent to continue in the hypertension control program until study completion in June 2025. Individuals who declined continuation were referred back to primary care clinics for routine care.

Statistical Analysis Plan

Implementation Evaluation of a Combination Intervention for Sustainable Blood Pressure Control in Rural KwaZulu-Natal, South Africa

Version: 1.0

Date: 20 October 2023

Written by:		Role:	Date:
Name	Lusanda Mazibuko	Trial statistician	
Signature			23 October 2023
Authorised by:			
Name	Kathy Baisley	Head, Data Science Unit	
Signature			
Name	Mark Siedner	Co-PI	23 October 2023
Signature			
Name	Thomas Gaziano	Co-PI	24 October 2023
Signature			

1. Overview of trial design & aims

IMPACT-BP is a randomised controlled trial to evaluate the effectiveness of community-based, technology-supported interventions to reduce systolic blood pressure (SBP) and improve blood pressure control among individuals with uncontrolled hypertension in rural KwaZulu-Natal. The study aims to identify the optimal strategy for blood pressure management in rural South Africa.

The study will compare three treatment strategies: 1) standard of care (SOC), clinic-based management of hypertension, 2) a community blood pressure monitor-based model, in which individuals receive blood pressure cuffs, and are remotely monitored by nurses via community blood pressure monitors (CBPM) and a mobile health-based clinical decision support tool, and 3) an enhanced community blood pressure monitor-based model that includes home-based blood pressure cuffs that transmit readings over cellular networks directly to clinic-based nurses (eCBPM+). In both intervention groups, CBPMs will visit participants to record (CBMP) or verify (eCBPM+) blood pressure readings, dispense medications, and relay instructions from clinic nurses.

2. Study endpoints

The trial aims will be evaluated through the primary and secondary outcomes below, as defined in the study protocol.

Primary outcome

- Difference between arms in change from baseline in systolic blood pressure 6 months after enrolment.

Secondary outcome

- Proportion of participants with blood pressure control at 6 after enrolment (defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg)

Safety measures

- Number of adverse drug reactions.
- Proportion of participations retained in hypertension care at 6 months.

Acceptability, fidelity, sustainability, and cost-effectiveness of the interventions will also be assessed; these objectives will be covered in a separate analysis plan.

3. Eligibility criteria

Study recruitment will occur at the Nkundusi and Madwaleni primary health care clinics (PHC) in the AHRI Health and Demographic Surveillance Site (HDSS). All adults who present to these clinics during weekdays will be screened for potential enrolment.

Individuals are eligible to enrol if they:

- Are age ≥ 18 years old
- currently reside in the catchment area of the enrolment clinics with plans to remain in the area for the next 2 years
- have elevated blood pressure (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mmHg) at screening
- have evidence of at least one previous elevated blood pressure reading in the medical chart 6 months ago or earlier, to meet criteria for hypertension in the South African Department of Health guidelines which require elevated readings on at least two occasions.

Exclusion criteria are

- pregnant women, confirmed by urine β -HCG testing on the day of screening for women aged <55 years, or breastfeeding women
- symptomatic hypertension and a blood pressure >180 mm Hg systolic or 110 mmHg diastolic
- advanced chronic kidney disease (GFR <60 ml/min/ 1.73m^2) as determined by point-of-care creatinine testing
- individuals on three or more anti-hypertensive medications at full dose

4. Randomisation

After informed consent, individuals will be randomised in blocks of 9 to one of the three study arms using the REDCap randomization module. Randomisation will be stratified by the clinic and active use of anti-hypertensive therapy at the time of enrolment.

5. Data collection

At enrolment, participants will be asked about sociodemographic characteristics, medical history and hypertension treatment history, self-reported medication adherence, quality of life, and resource allocation data to enable cost effectiveness analyses.

All participants will be followed up at 6 and 12 months after enrolment, where blood pressure will be measured by study nurses using a standardised Omron BP cuff. Blood pressure will be measured after the participant has been seated for 5 minutes. Three measurements will be taken on the same arm in the seated position, with each measurement taken 5 minutes apart. Data will also be collected on medication regimen changes and adherence, medical history including complications, hospitalizations and treatment side effects, and resource allocation, to enable estimates of program sustainability and longer term costs.

For participants who cannot be reached to schedule 6 or 12 month visits, a study staff member will attempt a home visit to collect outcome data.

6. Sample size

Based on patient attendance data from the two PHCs in our study in 2020, we estimate that there are over 1000 individuals with uncontrolled hypertension and thus eligible to enrol in the trial. We anticipate mean blood pressure at baseline will be 150/95 mmHg, with a standard deviation (SD) of 19 mmHg, based on previous studies. With 774 participants enrolled (258 per arm), we will have 80% power to detect a 5 mmHg difference between arms in the change of blood pressure from baseline to 6 months, assuming 20% loss to follow-up, a correlation between baseline and follow-up measurements of 0.5, and an alpha of 2.5% to account for multiple testing with comparisons between the SOC and both intervention arms (Table 1).

This same sample size will also give us greater than 80% power to detect an increase in the proportion of participants who achieve BP control (defined by a systolic BP <140 mmHg and diastolic BP <90mm Hg) at 6 months from 30% in the SOC arm to 45% in the interventions arms, or from 40% in the SOC to 56% in the intervention, also allowing for an alpha of 2.5% to account for multiple testing.

Table 1. Differences in change from baseline that can be detected with 80% power

N enrolled per arm	Loss to follow-up	Difference that can be detected (mmHg)	Standard deviation	Correlation between observations	Power
330	20%	5.0	19.0	0.20	80%
258	20%	5.0	19.0	0.50	80%
148	20%	7.5	19.0	0.20	80%
115	20%	7.5	19.0	0.50	80%

7. Definitions and analysis populations

All analyses will be conducted using the intention-to-treat principle, where all randomised participants will be included in the analysis regardless of adherence to the intervention.

All analyses of blood pressure will use the average of the second and third measurement as the blood pressure measurement for that visit. In the primary analyses, participants who are missing any of the three measurements will be considered to be missing blood pressure data for that visit. As a sensitivity analysis, individuals with fewer than three measurements will be included, using the average if there are two, or a single measurement if only one is available.

For outcomes that are based on data collected at the 6 month visit, the primary analyses will be restricted to participants with the relevant outcome data at 6 months (complete case). For outcomes that use data collected at both the 6 month and the 12 month visits, all participants with outcome data at either visit will be included (see section 10).

Sensitivity analyses will also be conducted where those with missing blood pressure data at a particular visit will be treated as having no change in blood pressure or having uncontrolled blood pressure. The primary analysis will be based on participants with complete blood pressure information; however multiple imputation of missing outcome values may also be used for exploratory analyses (see section 10).

For all outcomes, the primary analysis will be adjusted for clinic and active use of hypertension medication (i.e. the randomisation strata covariates) and blood pressure at baseline. Further, additional analyses adjusted for covariates that are known a

priori to be associated with blood pressure (e.g. age, sex, obesity, co-morbidities), or those that show baseline imbalance, may be conducted to explore the robustness of our results.

An interim analysis may be performed after all participants have completed their 6 month visit, since the primary outcome relates to this time. Data analysis will not begin until the database has been locked and the analysis plan has been signed.

8. Description of the cohort at baseline

In order to assess the comparability of the treatment groups, baseline characteristics of participants will be summarised by arm. Continuous variables will be summarised using means and standard deviations, and categorical variables will be summarised using frequencies and percentages. No formal statistical testing will be done.

Following the CONSORT guidelines, the number of individuals screened, the number who were eligible, and the number enrolled in the trial will be illustrated in a flowchart. Reasons for non-eligibility and non-enrolment will be tabulated. The flow chart will also show the number of participants attending the follow-up visits at 6 and 12 months, and the number withdrawing from the study, by trial arm.

The baseline characteristics of participants who are included in the analyses at 6 months (primary outcome) and 12 months and those who are not included (either because they withdrew, were lost to follow-up, or missed the relevant visit) will be summarised and compared descriptively.

9. Statistical methods

The statistical methods that will be used to address each study objective are described below. To correct for multiple testing when comparing the two intervention groups with the control group (SOC), we will use the Bonferroni correction with a significance p-value of 0.025

9.1 Primary objective

The primary objective of the trial is to examine the effect of the interventions on the change from baseline in systolic blood pressure 6 months after enrolment. The mean

and SD systolic blood pressure, and the mean and SD change from baseline, at the 6 and 12 month visits will be summarised by treatment arm.

Linear regression will be used to estimate the mean difference, and its 95% confidence interval (CI), between each intervention and SOC (i.e. CBPM vs SOC and eCBPM+ vs. SOC) in the change from baseline at 6 months. The response variable will be systolic blood pressure at 6 months; the model will include treatment arm, clinic, active use of hypertension medication and baseline systolic blood pressure.

In secondary exploratory analyses, we will adjust for baseline values of age, sex, body mass index (BMI), smoking status and HIV. In separate models, we will fit an interaction term between the treatment arm and sub-groups of interest (e.g. sex, age group, co-morbidities) to examine sub-group effect sizes and potential effect modification.

9.2 Secondary objective

The secondary objective of the trial is to examine the effect of the interventions on the proportion of participants with controlled blood pressure 6 months after enrolment.

The number and proportion of participants with controlled blood pressure (defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg) at the 6 and 12-month visits will be tabulated by treatment arm. Logistic regression will be used to estimate the odds ratio (OR) and 95% CI for the effect of each intervention on blood pressure control, compared with SOC. The model will include terms for treatment arm, use of hypertension medication, and clinic [randomisation strata].

9.3 Safety measurements

The number and proportion of participants with at least one adverse event (AE), and the total number of AEs, will be tabulated by the treatment arm. AEs will be tabulated by diagnosis, severity and relationship to the intervention.

The number and proportion of participants who are still in hypertension care 6 months after enrolment will be tabulated by the treatment arm. Retention in care will be defined as currently having sufficient BP medicine in possession (taking into account the date of last visit and the amount of medication dispensed), as the primary definition. As a secondary definition, retention will be defined as having seen a health care worker for

hypertension in the past 3 months. Logistic regression will be used to estimate the OR and 95% CI for the effect of each intervention on retention in hypertension care. The model will include terms for treatment arm, clinic and active use of hypertension medication at baseline.

10. Additional exploratory analyses

The effect of each intervention (vs SOC) on mean change from baseline in systolic blood pressure over 12 months will be estimated using a linear mixed model. The response variable will be systolic blood pressure (at 6 and 12 months); the model will include fixed effects for treatment arm, visit, a treatment arm-visit interaction term, randomisation strata (clinic and active use of hypertension medication at enrolment) and baseline systolic blood pressure, and participant as a random effect to account for correlation of repeated measurements within the participant. The inclusion of the interaction term allows the effect of the intervention to differ over time. If the interaction term is not statistically significant at $p < 0.10$, we will drop it from the model and estimate the overall effect of each intervention (vs SOC) on the change in systolic blood pressure during the trial.

The effect of each intervention (vs SOC) on blood pressure control over 12 months will be estimated using random effects logistic regression. The model will include fixed effects for treatment arm, visit, randomisation strata (clinic and active use of hypertension medication at enrolment) and treatment arm-visit interaction term, and random effects for the participant to account for correlation of repeated measurements. If the interaction term is not statistically significant at $p < 0.10$, we will drop it from the model and estimate the overall effect of each intervention on the blood pressure control pressure during the trial.

All participants with outcome data at either follow-up visit will be included in these analyses. Estimates from random effects models are valid under the assumption that the outcome data are missing at random conditional on the observed outcome at the non-missing visits, and other covariates in the model.

For participants with missing outcome data at month 6 or month 12, we may impute blood pressure measurements at those time points, using multiple imputation by

chained equations. Imputation models will contain observed blood pressure measurements, age, sex, BMI, smoking status, use of anti-hypertensive medication, HIV, clinic, treatment group and any covariates that are found to be associated with missingness.

The consistency of the effect of the intervention on the primary outcome will be assessed in the following pre-specified groups, using a statistical test of interaction. Effect estimates and 95% confidence intervals will be presented for each subgroup, plus the interaction p-value.

- Individuals with systolic blood pressure (SBP) ≥ 160 mmHg and those with SBP < 160 mmHg at enrolment.
- Individuals based on self-reported HIV status.
- Men and women
- Individuals aged ≥ 60 years and < 60 years.

References

1. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010; 340:c869.