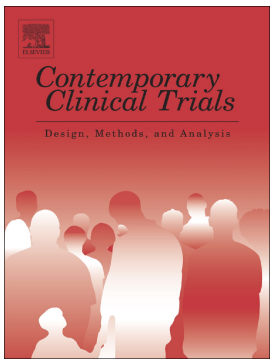
Protocol: Implementation evaluation of a combination intervention for sustainable blood pressure control in rural KwaZulu-Natal, South Africa (IMPACT BP): A three-arm, unblinded, parallel group individually randomized clinical trial



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Protocol: Implementation Evaluation of a Combination Intervention for Sustainable Blood Pressure Control in Rural KwaZulu-Natal, South Africa (IMPACT BP): A three-arm, unblinded, parallel group individually randomized clinical trial.

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Abstract

Background

Hypertension is the primary risk factor for stroke and heart disease, which are leading causes of death in South Africa. Despite the availability of treatments, there is an implementation gap in how best to deliver hypertension care in this resource-limited region.

Methods

We describe a three-arm parallel group individually randomized control trial to evaluate the effectiveness and implementation of a technology-supported, community-based intervention to improve blood pressure control among people with hypertension in rural KwaZulu-Natal. The study will compare three strategies: 1) standard of care (SOC arm) clinic-based management, 2) home-based blood pressure management supported by community blood pressure monitors (CBPM arm) and a mobile health application to record blood pressure readings and enable clinic-based nurses to remotely manage care, and 3) an identical strategy to the CBPM arm, except that participants will use a cellular blood pressure cuff, which automatically transmits completed readings over cellular networks directly to clinic-based nurses (eCBPM+ arm). The primary effectiveness outcome is change in blood pressure from enrollment to 6 months. The secondary effectiveness outcome is the proportion of participants with blood pressure control at 6 months. Acceptability, fidelity, sustainability, and cost-effectiveness of the interventions will also be assessed.

Conclusions

In this protocol, we report the development of interventions in partnership with the South Africa Department of Health, a description of the technology-enhanced interventions, and

details of the study design so that our intervention and evaluation can inform similar efforts in rural, resource-limited settings.

Introduction

Stroke is a leading cause of death and disability, particularly in low-income and middle-income countries like South Africa (1-3). Non-communicable diseases (NCDs) account for 70% of global deaths (4), and individuals living in resource-limited settings are 1.5 times more likely to die prematurely from these conditions than those living in high-income countries (5). Uncontrolled hypertension increases the risk of NCDs such as heart failure, myocardial infarction, kidney disease, and stroke (6-9). Hypertension treatment that results in lower, more optimal blood pressure readings can prevent cardiovascular diseases and improve morbidity (10, 11). However, there remains a substantial knowledge-implementation gap between the effective hypertension therapies and the effectiveness of health systems to provide hypertension control to the population (12).

In the rural province of KwaZulu-Natal, South Africa, one in six adults have hypertension, and fewer than one in four of those with hypertension have disease control (13). The KwaZulu-Natal health department's strategic goal of reducing the morbidity, mortality, and control of NCDs through increased screening and treatment (14) is in line with the South African Department of Health's "Strategic Framework 2019-2024" goal of increasing life-expectancy through universal health coverage (15). Against the background of efforts to strengthen health systems for universal health coverage and health equity, many African countries have been relying on community health workers to deliver primary health care services (16) in collaboration with clinic-based nurses. Community healthcare workers have positively impacted hypertension management programs in Argentina (17) illustrating that they can be utilised to assist in efforts to control NCDs. In South Africa, community-based programs consist of the primary care clinical outreach team, led by a nurse and comprising several community healthcare workers. Each team is attached to a primary care facility and provides services to individuals at household levels, however the community

healthcare workers are neither trained to take blood pressure measurements nor advise patients about hypertension-related lifestyle changes (18, 19).

The scientific goals of this project are to inform best practices for implementing interventions targeting health systems and individual barriers to effective hypertension care in rural KwaZulu-Natal. The NCD control program of the South African Department of Health (20) includes community-based delivery of care for chronic diseases, which has been shown to be effective in HIV care (21), and was given increased priority during the COVID-19 pandemic (22). To achieve improved blood pressure control, we have chosen a combination of interventions that target both the health system and the individual, and which have not been widely successful in health system translation in settings with limited resources. We conducted formative qualitative work to describe the experiences and care preferences of patients living with hypertension in rural KwaZulu-Natal. We also conducted pre-intervention interviews to assess the acceptability and readiness for the interventions and clinical trial among community healthcare workers, nurses, and provincial and district government officials. The outcome of the qualitative work informed the final intervention design of the clinical trial.

This protocol describes how we plan to conduct a randomized trial to evaluate the implementation of a community-based hypertension control program within the public healthcare sector in rural South Africa, which is comprised of three primary components: a) community-based disease management with home-based blood pressure measurements collected directly by patients; b) task shifting that includes routine visitation by local community blood pressure monitors (CBPMs) to record blood pressure measurements taken by patients, troubleshoot issues, communicate decisions from clinic-based nurses, and deliver medications and c) a mobile health application used by CBPMs to record and communicate blood pressure measurements to clinic nurses and to provide clinical decision support for

nurses to make treatment decisions. A similar approach was used by the Hope 4 clinical trial which was conducted within urban and rural communities in Columbia and Malaysia (23). In this trial, non-physician health workers were used to screen and enrol participants with new or uncontrolled hypertension from the community. Following community screening, the intervention included free antihypertensive and statin treatment suggested by non-physician health workers but under the supervision of doctors, treatment of cardiovascular disease risk factors by non-physician health workers using tablet computers-based simplified management algorithms and counselling programs. A difference between the Hope 4 study and ours is that our trial interventions are fully community-based with home-based blood pressure measurement, whereas the HOPE 4 trial used non-physician health care workers, but provided care through clinic-based facilities after initial community-based screening. We will conduct the clinical trial in partnership with the KwaZulu-Natal provincial Department of Health, who participated in the design and implementation of the intervention. Our specific study aim is to determine the effectiveness of a community-based, technology-supported intervention to reduce systolic blood pressure (SBP) and increase blood pressure (BP) control among individuals with uncontrolled hypertension. Our overarching scientific objective is to partner with the KwaZulu-Natal provincial Department of Health to identify an effective, scalable, and sustainable intervention to meaningfully address the hypertension epidemic in the country.

Methods

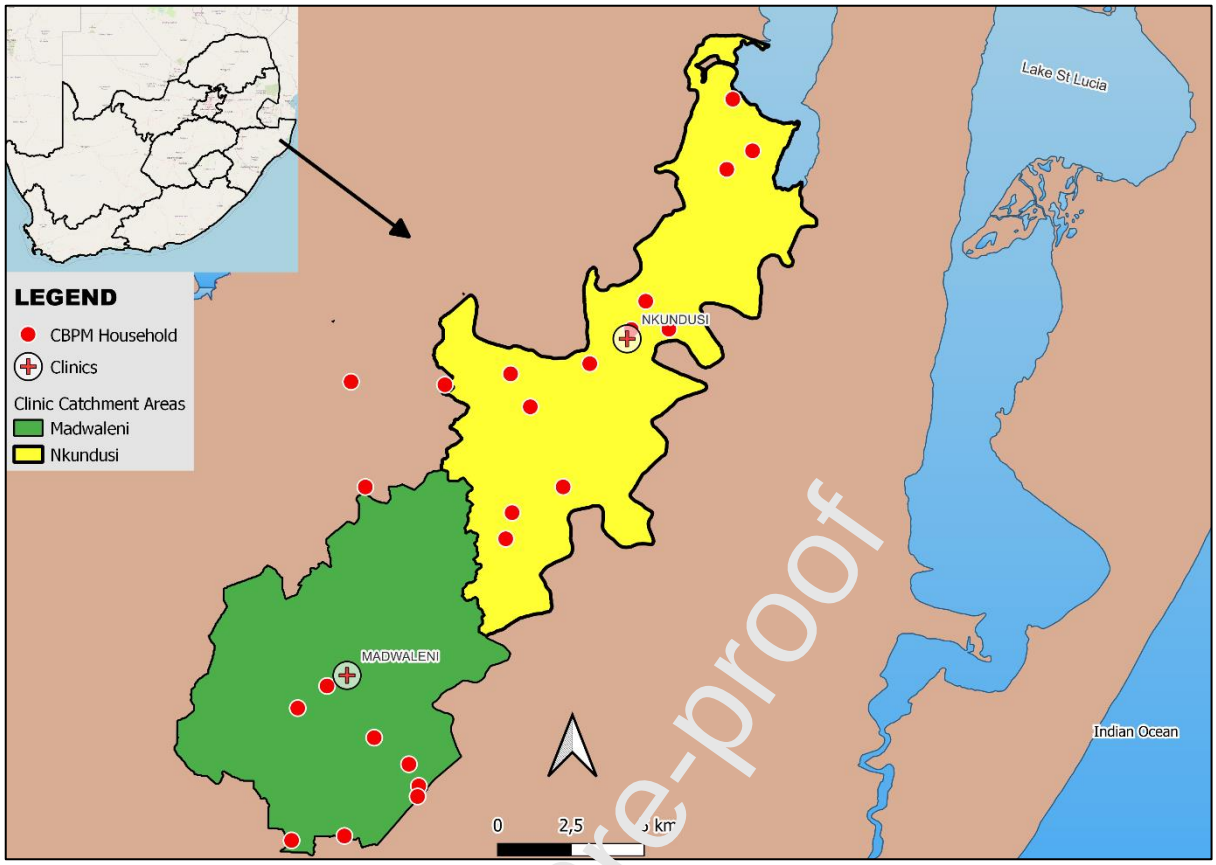
Study design

This is a three-arm, unblinded, parallel group individually randomized clinical trial that will compare three strategies of hypertension management in rural South Africa for individuals accessing care through the public health sector.

Recruitment and Screening

Participant recruitment will occur at public sector primary healthcare clinics in the uMkhanyakude District, KwaZulu-Natal, starting with Nkundusi and Madwaleni clinics **(Figure 1)**. These clinics are within the Health and Demographic Surveillance Site (HDSS), where clinic attendance information and homestead coordinates are integrated into an electronic data system for more than 120,000 residents. We will screen all adults who present to these clinics during weekdays for potential enrolment. Individuals will be eligible if they meet the following criteria: a) age 18 years or greater, b) currently residing in the catchment area of the enrollment clinics with plans to remain in the area for the next 2 years; c) elevated blood pressure (systolic blood pressure $\geq$ 140mm Hg or diastolic blood pressure $\geq$ 90 mmHg) at screening; and d) known diagnosis of hypertension or evidence of at least one prior elevated BP reading in the medical record within 6 months before screening, which meets criteria for hypertension in the South African guidelines (elevated BP readings on at least two occasions and up to 6 months of life-style counseling prior to initiation of medications in moderate hypertension (24)). We will exclude a) pregnant women, confirmed by urine β-HCG testing on the day of screening for women under the age of 55 years, and breastfeeding women, b) persons with symptomatic hypertension and a BP >180mm Hg systolic or >110 mmHg diastolic, d) those with advanced chronic kidney disease (GFR < 60 ml/min/1.73 m^2) as determined by point-of-care creatinine testing (25), and e) persons already receiving three or more anti-hypertensive medications at full dose. After confirming eligibility criteria, study nurses will obtain informed consent in the preferred local language of study participants (IsiZulu or English).

Figure 1. Study recruitment sites within the Health and Demographic Surveillance Site

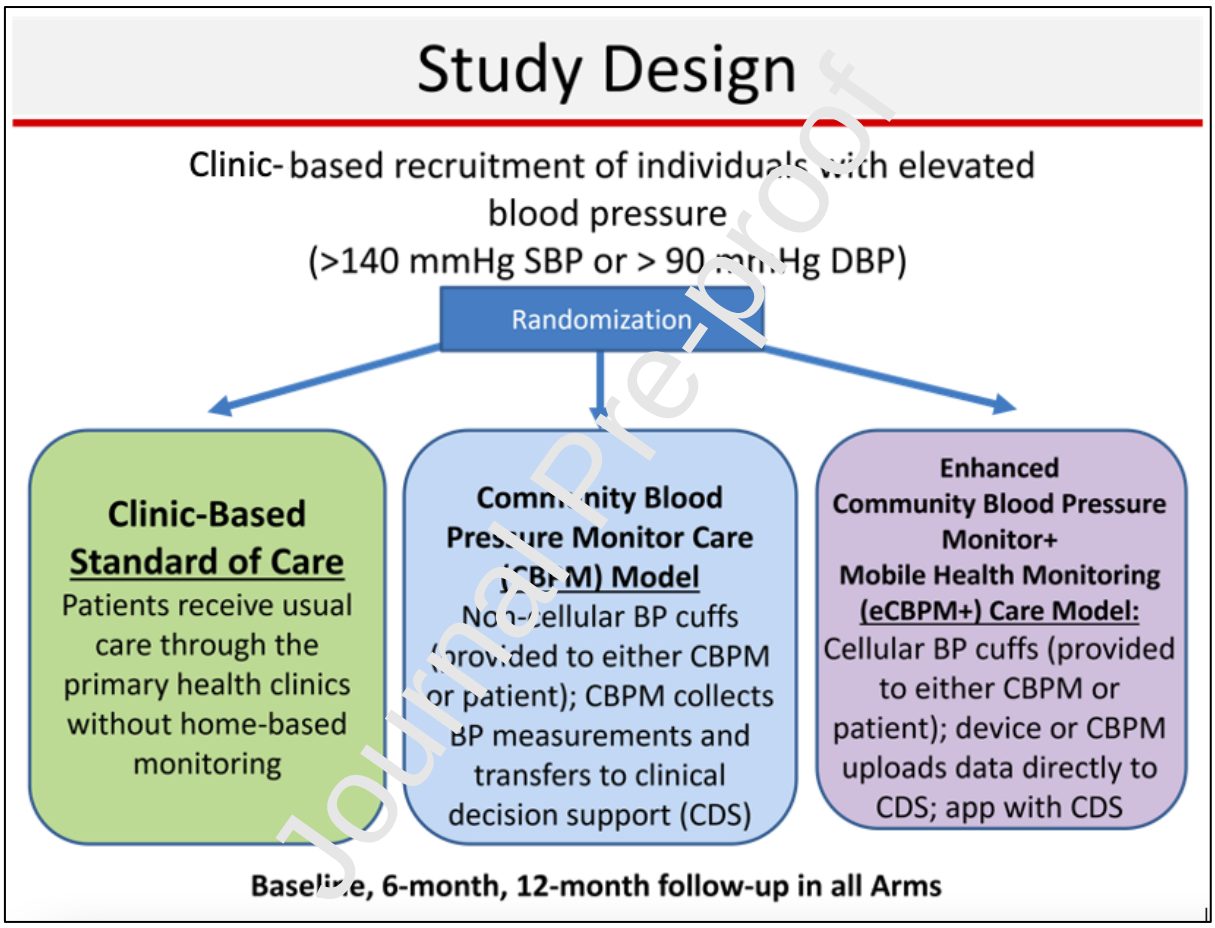


Randomization

Consenting participants will be randomized in blocks of nine, stratified by clinic, into one of three study arms: 1) standard of care (SOC), with routine, clinic-based management of hypertension by nurses, 2) CBPM-based strategy (CBPM), in which participants receive Omron blood pressure cuffs, and are remotely monitored by nurses with the help of CBPMs and a mobile health clinical decision support tool, and 3) an enhanced CBPM-based strategy that provides participants with cellular Blipcare blood pressure cuffs that transmit readings over cellular networks directly to nurses (eCBPM+) (**Figure 2**). The randomization table was generated by the study statisticians without access by study investigators or staff, and saved into the REDCap study database (26) which assigns participants to arms automatically after eligibility confirmation and completion of the informed consent process. Although individual randomization may risk "contamination" of the intervention between arms our health intervention is primarily home-based, reducing the risk of contamination common in

centralized clinic-based strategies. While the intervention may improve overall hypertension care, the SOC arm will not have access to home-based measurements, clinical decision support tools, or support from CBPMs, such as blood pressure measurements and medicine delivery.

Figure 2. Study Schema

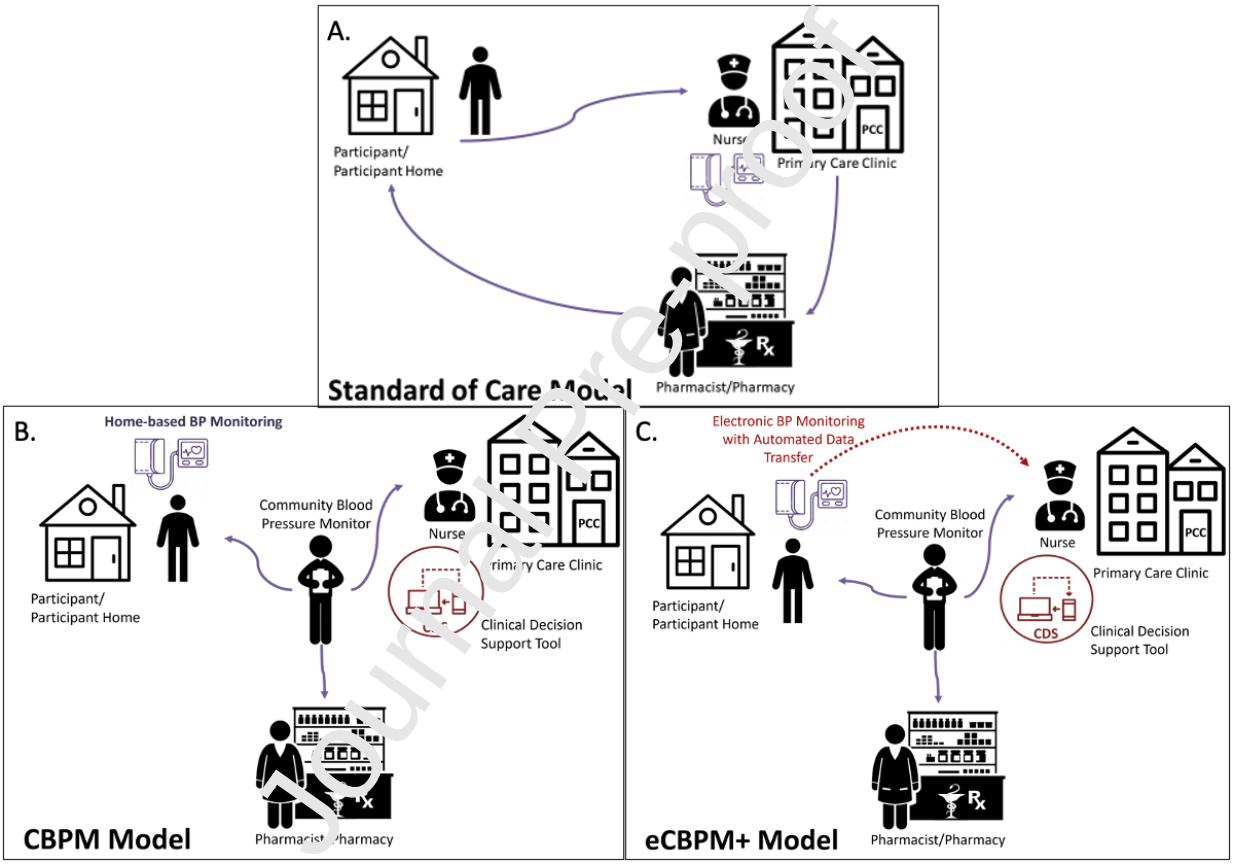


Standard of Care Arm

Participants randomized to the SOC arm **(Figure 3A)** will receive usual hypertension management at the clinic, according to the South African National Department of Health guidelines (24). Participants may be prescribed medication by the study nurse at their first enrollment visit and then will be asked to continue their follow-up clinic visits with the Department of Health nurse as recommended by the treatment guidelines. Routine care consists of monthly recommended visits to the clinic until the blood pressure is under control

(<140 mmHg systolic and <90 mmHg diastolic) and then at 6 monthly intervals. Blood pressure is measured by the nurses at clinic visits. Available medications that nurses can prescribe include those on the South African Essential Drug List (24), and involve the use of hydrochlorothiazide, enalapril and amlodipine. Prescriptions are typically collected by patients at the clinic on a monthly basis.

Figure 3. Depiction of each trial arm, including standard of care (A), community blood pressure monitor (CBPM) strategy (B), and eCBPM+ strategy (C)



Community Blood Pressure Monitor Arm

A key feature of the cooperative design is the employment of CBPMs by the study to conduct intervention study visits in participant homes, focusing primarily on hypertension management. The CBPMs were employed using the Department of Health hiring criteria for community healthcare workers. The CBPMs completed a training in community health management and hypertension care, including the following main topics: understanding hypertension, the causes of hypertension, the management of hypertension and how to measure hypertension. Prior to the trial, we performed formative work to learn about barriers and facilitators to hypertension care as well as preferences for intervention design through in depth interviews and focus group discussions with stakeholders (patients, nursing staff, community health workers, and Department of Health employees). Primary lessons learned, included: 1) clinics were over-burdened with long wait times; 2) equipment shortages were common; 3) nurses expressed a desire for more training/oversight; 4) community healthcare workers had to travel long distances and were over-burdened; 5) patients expressed long distance and costs to get to clinic.

In response to this, and with input from Department of Health and the South African Non-Communicable Disease Strategic Guidelines (20) which focus on community healthcare worker -based care, we finalized the intervention, to shift focus of clinical care from clinics to the community to decongest clinics, reduce wait times, reduce financial and time burden on patients, to empower community healthcare workers with time to do hypertension care through hiring of a cadre of CBPMs, providing nurses with support through a clinical decision support tool, and to replace clinic based cuffs with home-based measurement.

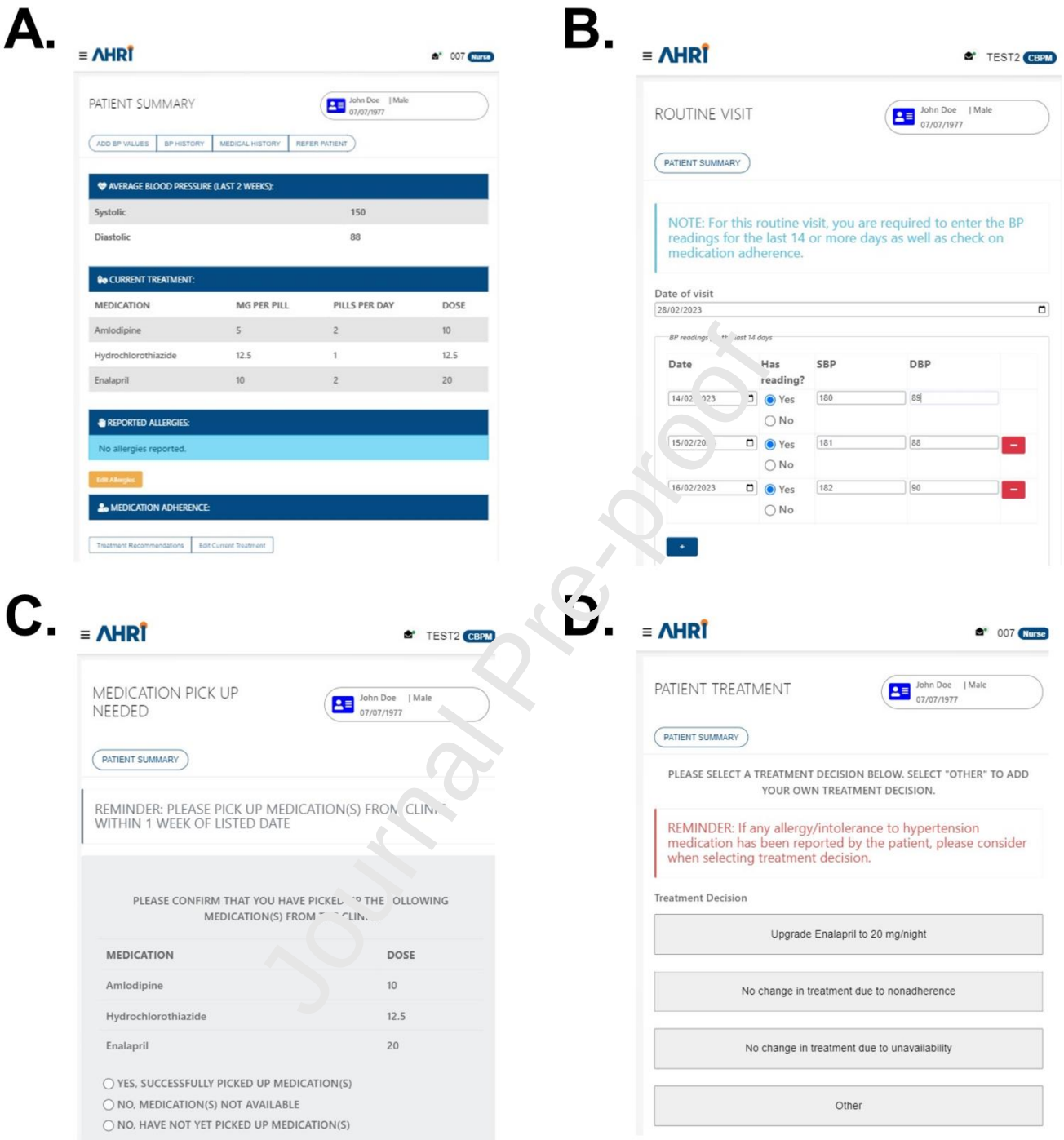
At enrollment, participants in the CBPM arm **(Figure 3B)** will be given an Omron blood pressure device, receive standardized operation training, and be assigned to be a CBPM. CBPMs are assigned in two ways: 1) if the participant is part of the demographic and health

surveillance site program operated by the Africa Health Research Institute (27), their homestead's map coordinates, which are available at the clinic, are used to assign him/her to a CBPM that is geographically closest and available or, 2) if the participant is not part of the demographic health surveillance program, then CBPMs are assigned a CBPM using their Isigodi (local area) residence. Participants in the CBPM will be instructed to take daily blood pressure measurements. These measurements will automatically be saved in the memory of the Omron device. CBPMs will visit participant homes every 2-4 weeks to collect blood pressure measurements and enter them into the Community Hypertension Care mHealth Application (see below for further details about the application), assess for hypertension symptoms, and discuss treatment adherence and educate on hypertension reduction lifestyle recommendations. CBPMs will visit the clinic once weekly to meet with supervising nurses and review patients in their mutual care. They will also collect prescriptions at the clinic to deliver them to patients each time a new prescription is written by the nurses. Similar to the SOC arm, medications available in the CBPM arm will be provided by the clinics and included in the South African Essential Drug List.Once a participant's hypertension is deemed to be under control, the prescription length can be increased from 30 days to 90 days, keeping with Department of Health guidelines.

Both community based monitoring arms are supported by a mobile health application, Community Hypertension Care mHealth Application. The application allows CBPMs to capture home-based blood pressure data, promotes communication between the community health team members and the Department of Health nurses, and supports nurses in using the treatment recommendations as outlined in the South African hypertension guidelines. The CBPM interface of the application allows for input of blood pressure readings and recording of home visits and prescription drug pick up/drop off (**Figure 4).** It also sends automated reminders to CBPMs regarding home visit appointments and overdue prescripitions. There is

a separate nursing interface which includes a dashboard showing their assigned patients and their designated CBPMs, alerts to review clinical data, and a Clinical Decision Support System (CDSS) that makes recommendations about treatment regimens based on the the South African hypertension guidelines **(Figure 4).** The nurse interface also includes alarms for urgent clinical issues, such as elevated BPs >180/110 mmHg for two consecutive days or any reading >220/120 mmHg).

Figure 4. Example screenshots from mobile health application



The application stores and displays summaries of patient demographic, clinical and therapeutic history (A); an interface for community blood pressure monitors to enter blood pressure readings during home visits (B); reminders for both community blood pressure monitors and nurses to conduct scheduled tasks such as home visits, clinical decision making, and prescription refills (C); and a nursing decision support tool, based on South African Department of Health guidelines, to help guide therapy selection based on the recent blood pressure readings, the current regimen, and treatment and allergy history (D).

*Enhanced Community Blood Pressure Monitor with Mobile Blood Pressure Monitoring (*eCBPM+) *Arm*

Participants randomized to this arm will alse be treated according to South African hypertension guidelines. In addition, and similar to those in the CBPM arm, participants in the eCBPM+ arm **(Figure 3C)** will also be assigned a CBPM and given a home blood pressure cuff. In this arm, the BP cuffs will include cellular network capability (Blipcare, Carematix, Chigaco, IL) that directly transmit blood pressure readings to the mobile health application. Participants in this arm will be instructed to take daily blood pressure measurements, which will be automatically uploaded onto the server to be made available for the Department of Health nurse to make clinical decisions based on the readings. CBPMs will return to participant homes every 2-4 weeks to ensure the functionality of the devices and proper transmission, attend to troubleshooting issues, assess for hypertension symptoms, and discuss treatment adherence and lifestyle recommendations. The Department of Health nurses at the clinics will use the CDSS application to review transmitted blood pressure data, communicate with CBPMs, and make treatment decisions. After the nurses make treatment decisions, the CBPMs will receive requests via the application to pickup prescribed medications at the clinic and deliver them to the homes of participants. Participants who achieve optimal blood pressure control may have the time between their visits lengthened, if recommended by the Department of Health nursing champion.

Study Visit Schedule and Data Collection The full study data collection schema is described in **Table 1**. At enrollment, participants complete questionnaires to capture data on sociodemographic charateristics, medical history and hypertension treatment history, self-reported medication adherence, quality of life, and functions performed to capture resource allocation data for planned cost effectiveness analyses **(supplemental appendix)**. Study staff

will conduct follow-up visits at participants' homes in all three study arms 6 months after enrollment. A study nurse will obtain an independent set of three BP measurements using standardized Omron BP cuffs for participants in all three study arms at baseline, 6-month, and 12-month visits independent of the CBPM program. These measurements will be taken while the participant is seated and at five minute intervals (28). At the 6-month visit, we will also collect additional data on medication regimen changes and adherence, medical history including complications, hospitalizations and treatment side effects, and resource allocation. We will conduct a final study visit in all three arms at 12 months after enrollment, to collect similar data as the 6 month visit to enable estimates of program sustainability and longer term costs. Potential adverse effects are captured both 1) passively where any participant can report an adverse effect to clinic or study staff which is recorded in the study database or 2) actively with questionnaires during the 6- and 12-month study visits. A study staff member will attempt a home visit to collect outcome data for participants who cannot be reached to schedule 6 or 12 month visits.

Table 1. Summary of Study Visit Procedures

	Enrollment Visit	6-Month Visit	12-month Visit
Screening and eligibility form	✓		
Consent form	✓		
Point of care creatinine	✓		
Sociodemographic questionnaire	✓		
Tracking form	✓		
Hypertension KAP	✓	✓	✓
Medication adherence	✓	✓	✓
Hypertension treatment history	✓	✓	✓
Resource use form	✓	✓	✓
Health related quality of life	✓	✓	✓
Blood pressure measurements	✓	✓	✓
Medication and laboratory history	✓	✓	✓
Adverse Event Form			
Study Outcome Form			✓

Study Effectiveness Outcomes and Statistical Analyses

The primary effectiveness outcome is the change in mean systolic blood pressure from baseline to 6 months between the three study arms. The secondary outcome is the proportion

of participants with controlled blood pressure, defined as SBP <140 mmHg and a diastolic BP <90 mmHg, at 6 months after enrolment. We will use linear regression to compare the change in systolic blood pressure from baseline to 6 months between the three arms. The response variable will be systolic blood pressure at 6 months; the model will include treatment arm, clinic & use of hypertension medication (i.e., randomization strata) and baseline systolic blood pressure. We will then use logistic regression to estimate the proportion of participants reaching blood pressure control. The primary analysis will be an intention-to-treat analysis. The characteristics of participants who are lost to follow-up will be documented by study arm. Participants with missing outcome data will be excluded from the primary analysis. We will perform sensitivity analyses in which participants with missing BP measurements will be treated as having no change in systolic BP and uncontrolled BP, or accounted for through multiple imputation. Furthermore, we will conduct subgroup analyses by gender, HIV serostatus, and baseline blood pressure, because they could potentially modify the effectiveness of the interventions. This is an open label study and therefore the study statistician is not blinded to study arm allocation.

Data Monitoring

The Data Safety Monitoring Board (DSMB) for the IMPACT-BP study is an independent committee that oversees safety, efficacy, and data integrity of the trial, maintaining strict confidentiality while ensuring adherence to guidelines. The DSMB charter has established that the DSMB will meet to review study safety data after 50% enrolment and make recommendations to the study team on continuation, modification, or early discontinuation of the protocol.

Power Calculations

For a power of 80%, 774 participants (258 per arm) are required to detect a 5mmHg difference in blood pressure change between arms, with assumptions of a 20% loss to follow-up, correlation between baseline and follow-up measurements of 0.5, and a two-sided alpha level of 2.5% to account for multiple testing in comparison between each intervention arm versus SOC.

Implementation Outcomes

To comprehensively evaluate the blood pressure intervention program, we will assess its fidelity, sustainability, acceptability, and cost-effectiveness in addition to our primary effectiveness outcomes using the Conceptual Model for Implementation Research and the Theoretical Framework for Acceptability. Approximately 12 months after the trial commences, key informant interviews will be conducted with study participants, study personnel, and Department of Health staff. Where appropriate we will include the same individuals interviewed prior to the start of the trial to compare their experiences during the trial with their initial expectations and preferences. This qualitative data will be combined with quantitative data to assess fidelity and sustainability of the intervention. Fidelity assessments will be conducted at 6 and 12 months after study enrollment, and based on monthly data collection using intervention clinic checklists to estimate adherence, exposure, and quality of the intervention. Using the CVD PREDICT microsimulation model (29), the cost-effectiveness of the intervention will be calculated as incremental costs for absolute changes in blood pressure (costs/mmHg) and incremental costs per extra participant with controlled blood pressure. Evaluation of these intervention pillars ensures that interventions are effective, feasible, and sustainable in real-world settings, such that policy-makers can make informed choices about allocating resources.

Ethical Review

The study protocol and informed consent forms are available in the **supplementary appendix**, and were reviewed by the University of KwaZulu-Natal's Biomedical Research and Mass General Brigham's Ethics Committees. This study was approved by the South African Health Products Regulatory Authority (SAHPRA Trial Number: N20211201) and also registered with the South African Clinical Trials Registry (SANCTR Number**:** DOH-27-112022-4895)

Discussion

Despite the widespread availability of low-cost effect therapies and prolonged health system efforts to improve hypertension control in resource-limited settings through nurse-initiated care, hypertension and its associated complications remain a significant contributor to non-communicable deaths (30). In response to this implementation gap, we designed and now seek to test an intervention based on local health system priorities, formative work with stakeholders, and prior regional successes in chronic disease care based on task sharing with community healthcare workers (31). In this protocol, we provide a detailed description of the technology-enhanced interventions and study design, developed in partnership with the South African Department of Health, with the goal of informing and guiding similar efforts in rural, resource-limited settings.

Our clinical trial was designed and implemented in partnership with the Kwa-Zulu Natal provincial Department of Health, with their involvement beginning with the protocol development stage, extending to the structure of the intervention, and the use of their nurses and community healthcare workers. We hope that this collaboration and community support will increase the chances of success of the intervention by incorporating local guidelines and

priorities into intervention design, while also promoting sustainability if the intervention proves to be effective. The choice of using community-based care was derived directly from their input and South African National Strategy to promote community-based care for chronic diseases (20). We also based all treatment algorithms on both the national primary care guidelines and the availability of medicines on the essential drug supply list. Finally, formative work during the design stage led to multiple alterations to our protocol. For example, interviews with Department of Health stakeholders revealed community healthcare worker job criteria that were used for project recruitment, including: 1) residing within the clinic catchment areas, 2) attainment of at least a grade 8 or above school level, 3) prior experience as a trained community healthcare worker or active voluntary service in the community, 4) the ability to travel to participants' homes and the local clinic and 5) possession of a home-based care certificate. Project community healthcare workers were subsequently designated as CBPMs and will receive the same salary as the Department of Health community healthcare workers to prevent any potential employer-changing behavior by the latter.

Design of our community-based intervention also highlighted the need for an application to promote communication between patients, CBPMs and the clinic-based nursing team across a large clinic catchment area. We developed a mobile health application, drawing upon lessons from previous remote hypertension management programs that were effective in large integrated health systems in the United States (32-34). These programs utilized patient-initiated home BP monitoring, medication titration through cellular technology using standardized algorithms, and task shifting. We used these features as a foundation for our interventions, but adapted them to be used in rural, resource-limited settings based on principles of ease of use, perceived usefulness, and technology acceptance (35). For example,

our application includes a graphical user interface tailored to the role of each study member, clear messages for reminder alarms, and clinical recommendations based on the three most commonly prescribed antihypertensive medications from the South African guidelines. The recommended medication choices, listed in order of clinical preference, generated from initial excel-based algorithm spreadsheets, were incorporated into the application and comprehensively validated through an iterative process. Moreover, the application includes an option to refer complex cases of hypertension to physicians for further management when the nurse-led management threshold has been met (i.e. persistent hypertension despite a treatment regimen of three medications at the maximum doses based on treatment guidelines).

Study results will be presented to the scientific community through conference presentation and peer reviewed, open access journal publication. We will also submit results to the Department of Health both directly and at the annual KwaZulu-Natal Research Day, and present and discuss our findings through a post-study stakeholder meeting. Finally results will be presented to the KwaZulu-Natal Community in partnership with the Africa Health Research Institute Community Engagement Unit through standing road shows and radio shows.

The proposed intervention has several potential benefits, including de-centralizing chronic disease care from the clinic to the community to minimize patient burden and decongest clinics, improving quality of care through electronic data capture of BP data and medication history, facilitating communication between patients and members of the healthcare team, promoting medication and BP monitoring adherence through regular CBPM visits, and ensuring guidelines based treatment care through an automated CDSS. If effective, this

community-based approach could provide a comprehensive framework for managing other chronic conditions, such as diabetes and obesity, leading to an integrated multimorbidity care model consistent with the South African strategic goals to increase life-expectancy through universal health coverage and promoting community-based care (15). The combination of remote, guidelines-based algorithmic management paired with community-based healthcare workers as described, have the potential to alleviate nurse workload, increase access to care among community members, and improve healthcare quality in rural South Africa. Finally, our partnership with the Department of Health to design and implement the program, along with a comprehensive implementation evaluation to include sustainability, fidelity, and cost-effectiveness will promote larger-scale adoption of the intervention if proven effective.

Declaration of Interests

The authors declare no conflicts of interest.

Access to Data

Data and the data dictionary defining each field will be available at https://data.ahri.org/index.php/ via the Africa Health Research Institute Data Repository. Please email RDMServiceDesk@ahri.org. Access will be granted after publication and upon approval of the proposed analyses by the IMPACT BP Scientific Steering Committee and completion of a data access agreement.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: