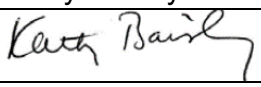
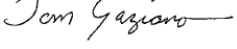
Statistical Analysis Plan

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

ClinicalTrials.gov registration Number: NCT05492955

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.

<u>Primary outcome</u>

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

<u>Secondary outcome</u>

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

<u>Safety measures</u>

- 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 >140mm 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 >180mm 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.