# Cardiovascular Disease Risk Reduction: A comprehensive package for the reduction of risk in Sindh, Pakistan

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### Introduction

Targeting the considerable burden of NCDs, affecting the poorest billion of the world, forms a key goal in global policies and plans.[1] However, most LMICs lack the fiscal and human capacity to address NCD-associated health, economic, and social burdens, posing barriers to the achievement of Sustainable Development Goals (SDGs).[2] In Afghanistan and Pakistan, the rapid increase in NCD-related morbidity and mortality represents a critical challenge (see figures below from the GBD visualization tool).[3] In health systems and policies traditionally geared towards communicable diseases and maternal/neonatal disorders and heavily battered by the diversion of resources to manage regional conflicts; the enormous threat of NCDs, especially cardiovascular diseases (CVD), type-2 diabetes (diabetes), and common mental disorders (CMD) remains largely unaddressed.[4]

According to the 2018 WHO progress report, an average person in Pakistan between the ages of 30-70 carries a 25-30% risk of premature death from NCDs. Yet, Pakistan has inadequate national system responses to NCDs. Locally relevant, high-quality data and empirical evidence on the effectiveness and cost-effectiveness of interventions addressing NCDs are scarce. The evidence gap exists both for population-level and individual-level interventions.

A recent study estimated that among low and middle-income countries (LMICs), India and Pakistan are most likely to suffer from CVD deaths in the future.[5] In addition to mortality, CVDs and NCDs also lead to a substantial increase in morbidity with a serious decrease in quality of life.[6] The high mortality and morbidity rates associated with CVDs emphasise the urgent need for effective prevention and management strategies to improve public health outcomes. Most of this burden of deaths and morbidity can be prevented by controlling common risk-increasing factors, most importantly hypertension,[7] as well as behavioural risk factors such as tobacco use, unhealthy diets, and lack of physical activity through adopting large-scale population-wide strategies. Control of obesity, hypertension, hyperglycaemia, and hyperlipidaemia along with low sodium intake, regular exercise and a healthy diet helps prevent the risk of CVDs.[7]

Addressing the prevention and control of NCDs and CVD requires a multi-faceted approach that targets diverse populations across different settings. In some populations we have interventions that have been proven to be effective but have not been implemented for example in rural communities the COBRA-BPS trial has shown the effectiveness of a multi-component hypertension intervention (MCHI) in reducing blood pressure.[8] However, the findings of this work have not translated to change in practice on the ground suggesting the need for implementation research to examine the best ways to implement this intervention in the real world.

In other target populations such as school-going children where early interventions may stem the rise of NCDs and understanding the risk of other populations that may be high risk such as certain occupational groups, there is little evidence from Pakistan and formative research

needs to be done to be able to design potentially low cost and effective interventions. Therefore, in this work package, we propose three studies with the overarching long-term goal of CVD risk mitigation in our communities. These studies range from implementation studies to early formative research: implementation trial in the community, a workplace-based study, and a qualitative investigation focused on school-going children. In the following sections, we describe the different studies and approaches. Each study will be led by a senior and early career investigator from AKU, and input will be provided by our Centre Collaborators from Khyber Medical University (KMU) and the University of York. This overarching risk reduction package aims to explore and implement interventions across three distinct components comprehensively. By examining these different dimensions, we strive to improve cardiovascular health outcomes in various population groups.

The first component of this study focuses on hypertension. High blood pressure is a major risk factor for CVDs and contributes to a significant burden of disease worldwide and there is a paucity of community-based behavioral interventions to address its burden in rural populations in developing countries. One such community-based intervention to address hypertension has been previously found to be effective in the Pakistani context in a cluster randomized controlled trial.[8] However, the findings and the approach tested in this study have not been scaled-up in Pakistan. Hence, in the present work, we aim to assess the impact of this evidence-based intervention when implemented at scale in rural communities.

### An Implementation Science Cluster Randomised Controlled Trial of a Community-Based Intervention for Managing Hypertension

#### Research questions

1. What are the perceived barriers and drivers to scaling-up a community-based multicomponent hypertension intervention (MCHI) within a public health system for adults with hypertension living in rural Sindh, Pakistan?
2. What strategies are needed for the adoption, implementation and maintenance of the MCHI when delivered at scale?
3. Compared to scaling up MCHI on its own, what is the effectiveness and cost-effectiveness of scaling up MCHI in combination with a set of implementation strategies in:
    a. Improving its adoption, implementation and maintenance?
    b. Lowering blood pressure in adults with hypertension?
4. What are the barriers and drivers observed while scaling up MCHI (both, with and without implementation strategies), which could guide further adaptations and tailoring of its scale up?

Hence the objectives of this study are:

- To identify implementation strategies for scaling up a proven community based multi-component hypertension intervention (MCHI) using implementation research frameworks

- To assess the effect of adding implementation strategies to community based MCHI in improving access to evidence-based hypertension care and on lowering blood pressure in adults with hypertension.
- Assess the cost effectiveness of implementation strategies to community based MCHI in improving access to evidence-based hypertension care on lowering blood pressure in adults with hypertension.
- To explore barriers and drivers observed while scaling-up MCHI to guide adaptation and tailoring of scale up

Methods

## Study design

This study follows the MRC framework for developing and evaluating complex interventions.[9] Specifically, the focus is on the implementation phase of the framework.[10] This is because there is an intervention (MCHI) that has already been proven effective and cost-effective in a large, high-quality multicountry RCT.[8] However, despite this trial being conducted and disseminated in Pakistan, this evidence-based intervention has not been scaled up. Moreover, there is equipoise regarding the effects of implementation strategies on the adoption and maintenance of the MCHI when delivered at scale.

The study will have three phases: Phase 1 will address research questions 1 & 2, Phase 2 will address questions 3a and 3b, and Phase 3 will address question 4.

## Phase 1: Barriers and Facilitators to Scale Up & Implementation Strategies

In this phase, we will identify potential barriers and drivers to scaling up MCHI in rural public health facilities in Sindh. Then, we will select implementation strategies to address these potential barriers and strengthen potential drivers.

The updated Consolidated Framework for Implementation Research (CFIR)[11,12] and the Expert Recommendations for Implementing Change compilation (ERIC) [13] (Appendix-1) will underpin our proposed work. The following activities will be conducted.

To better understand the potential barriers and drivers for implementing MCHI at scale in public health facilities, we will be conducting a series of workshops. Two sets of workshops will be held in each district (4 in total). Primary health service providers, including district health officers, district NCD focal persons, district Lady Health Workers (LHW) programme coordinators, LHWs and general practitioners will be invited to attend. A researcher trained in implementation science will facilitate these workshops, with a focus on identifying potential barriers and facilitators to scale up first and then the implementation strategies. We understand the importance of power imbalances and will ensure expert facilitation to address

any issues that may arise. Additional support will also be provided to workshop participants as needed.

During the first set of workshops, attendees will receive a list of short descriptions of potential barriers and drivers based on CFIR construct definitions.[13] They'll then be requested to evaluate the probability of facing each barrier/driver and their possible effects. Through the modified Delphi technique, they'll converge to a final list of the most important barriers/drivers (highly probable with significant effect) after 2 to 3 iterations.

Prior to the second set of workshops, CFIR-ERIC Mapping Tool[13] will be utilized to generate a list of potential ERIC strategies that can be evaluated to address each CFIR barrier and strengthen each driver identified in the first set of workshops. During the second set of workshops, participants will be required to select and rank up to 7 strategies that would be most effective in addressing each CFIR barrier/driver. ERIC strategies will be chosen based on the relevance of the strategy to the CFIR barrier, perceived improvement opportunities, and feasibility. Only those strategies that receive an endorsement of level 1 (by 50% or more participants) or level 2 (by 20%-49.9% of participants) for at least one CFIR barrier/driver will be included in the final list. Subsequently, these strategies will be categorized into three levels based on their feasibility: Level 1 strategies that are easy to implement and only require a change in processes, Level 2 strategies that require changes in the infrastructure, and Level 3 financial strategies.

## Phase 2: Effectiveness and Cost-effectiveness of the Implementation Strategies.

To investigate the effectiveness and cost-effectiveness of MCHI when delivered at scale, we will conduct a Type III effectiveness-implementation hybrid trial (Flowchart 1).[10] Given that MCHI targets its population through community health workers and health facilities, a cluster-randomized controlled trial design is chosen.

## Study setting

The trial will take place in Thatta and Matiari, two rural districts located in the province of Sindh, Pakistan. Thatta has a predominantly rural population of approximately 1 million people, with 82% residing in rural areas. This district is divided into four sub-districts, also known as talukas. Similarly, Matiari is a rural district with a population of 0.77 million people, of which 76.2% live in rural areas. It is administratively divided into three talukas. The public sector health infrastructure includes primary, secondary, and tertiary healthcare facilities, as well as a group of LHWs. These LHWs are associated with primary healthcare facilities such as Basic Health Units and Rural Health Centres. With each Basic Health Unit, there are usually 3-13 (an average of 5) LHW affiliated and they cover its entire catchment population, roughly 250 households/LHW.

In this trial, a cluster equates to a Basic Health Unit (BHU) and its catchment population. Each cluster will have , at least 1-2 LHWs , providing essential public health services to the entire population. These clusters are situated within Union Councils, which are contiguous

administrative units. Each Union Council will have at least one BHU. Initially, 30 Union Councils will be purposively selected in the two chosen districts. There are approximately 42 BHUs across both the districts. Eligible clusters will be identified using the following criteria:

► Identification of BHUs where LHWs are present and functioning.

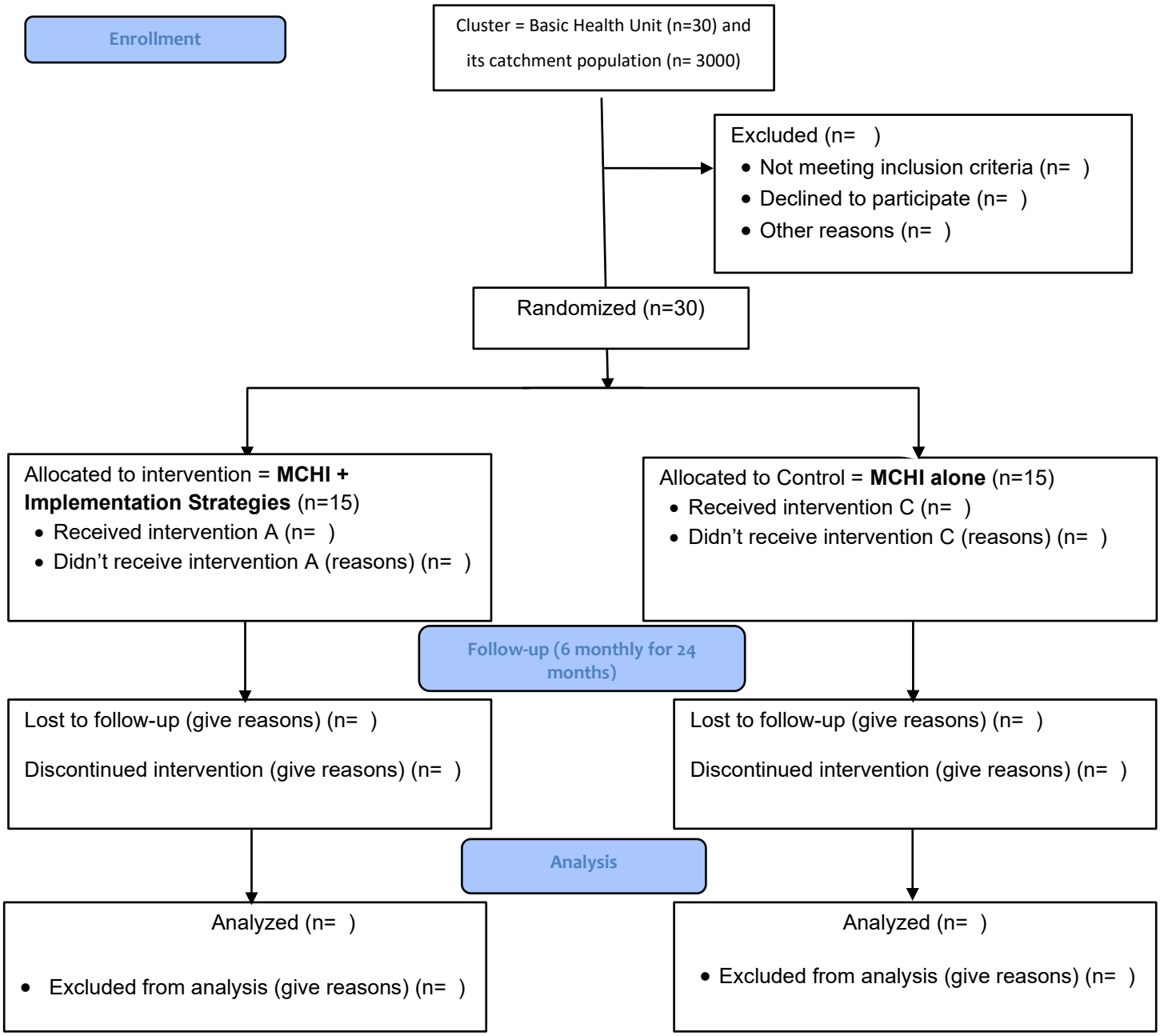
► A list of LHWs attached to each BHU will be obtained.

► Random selection of one LHW from each cluster (BHU) and the adjacent area will be undertaken to have a catchment of 200–250 households.

An eligible cluster will then be identified within each Union Council,. The distance of each cluster from its corresponding BHU will be determined using a GPS device.

These clusters will be stratified into two strata based on their distance from the respective BHU, which will be used in stratified randomization. The randomization will be stratified by districts as well as by the distance from the BHU, and the clusters will be randomly assigned in a 1:1 ratio to either MCHI + implementation strategies (the intervention arm) or MCHI alone (the control arm) using a computer-generated randomization programme at AKU.

Flowchart 1: The MCHI Implementation Science Trial



## Participants

*Inclusion criteria*

1) Are of age ≥35 years
2) Residents of the selected clusters
3) Have hypertension defined as
    (a) either with persistently elevated BP (SBP ≥140 mm Hg or DBP ≥90 mm Hg) average of last two of three readings from two separate days, where BP measurements on the same day were measured at least one minute apart
    (b) Diagnosed previously by a physician as hypertensive and/or on antihypertensive medications.

*Exclusion criteria*

Pregnant women and persons with advanced illness (e.g., those receiving dialysis or with liver failure), cancer, or an inability to travel to the clinic or unwilling/unable to provide consent will be excluded.

*Identification, eligibility assessment, consent and enrollment*

Our first step will be to obtain a list of all adults living in households within the selected clusters from the District Health Office. Once we have received appropriate permissions from the community gatekeepers, such as councillors, LHWs and field research team will visit jointly to all targeted household and update Household list (Appendix: 2a English, 2b Sindhi). After obtaining written consent (Appendix: 7.2a English, and 7.2b Sindhi) the field team will then screen out all 35 years and above individuals in the target households for hypertension and other chronic diseases including ischemic heart disease, diabetes, kidney disease and the risk factors using a structured questionnaire (Appendix: 8c English, 8d Sindhi). LHWs will also chase the same participants for hypertension screening independently. (Appendix: 3a English, 3b Sindhi). Blood pressure (BP) will be measured three times using a calibrated automated Blood Pressure Monitor with the individual in a sitting position. The readings will be taken one minute apart. Individuals with elevated BP (SBP ≥140 mm Hg or DBP ≥90 mm Hg) of the last two of three readings on the first visit will be revisited after 2 weeks for re-measurement of BP to confirm hypertension (Appendix: 4a English and 4b Sindhi). Those with persistently high blood pressure at the second screening visit will be invited for enrollment. Those who already on antihypertensive medications will be enrolled during the first visit. As part of the duty of care, all participants with elevated BP will be requested to see a trained general practitioner (GP) (Appendix: 5a English, 5b Sindhi). Those with very high BP (SBP ≥180 mm Hg or DBP ≥120 mm Hg) will be facilitated to receive an urgent hospital appointment.

# Health Facility Assessment Survey

This observational Health Facility Assessment survey will be conducted in 30 selected health facilities (BHUs/RHCs) across District Thatta and Matiari. An essential component of this

assessment is evaluating the referral mechanism in place at the surveyed facilities. Effective referral systems ensure that patients receive timely and appropriate care at higher-level healthcare centers when necessary. The survey will examine whether standardized referral guidelines exist and are adhered to, how patients are referred from BHUs/RHCs to secondary or tertiary care facilities, and the availability of transportation, such as ambulances, for referred patients. The findings will help strengthen referral linkages between PHC facilities and higher-level care centers, ensuring that patients receive the appropriate level of care without unnecessary delays. This, in turn, will contribute to better health outcomes and more efficient healthcare service delivery.

Project Research Associates will receive training on the pre-designed data collection tool (Appendix-13) and will gather information using RedCap software. Data analysis will be conducted using standard statistical methods as outlined in the original protocol.

## Interventions

The MCHI will be scaled up in both trial arms; however, the implementation strategies will only be introduced in the intervention arm.

*Multicomponent hypertension intervention*

The MCHI is a community-based intervention to reduce BP in people with hypertension and consists of the following components:

1. BP monitoring and stepped-up referral to a trained GP using a checklist at 3-month intervals, every LHW will be provided with a digital BP apparatus and will monitor the BP of the study participants enrolled in the study. The LHW will also be completing a BP monitoring checklist following the recording of participants' BP. Those participants with hypertension and/or poorly controlled BP (Systolic Blood Pressure (SBP) ≥160 mm Hg or Diastolic Blood Pressure (DBP) ≥100 mm Hg) at any visit will be referred to a trained general practitioner (GP) for the management of hypertension. For each referral, LHW will be completing a GP referral checklist having patient details, his/her BP readings, and other relevant details.

   **Home health education (HHE) delivered by LHWs:** Training of LHWs will be conducted in conveying home health education (HHE) to the adult hypertensive population using a structured behavior change communication approach. The training will be for 5 days, followed by a refresher training in 3 months and then annually. The curriculum of HHE will be based on the manual developed as part of the MCHI trial. The health messages will largely be focused on hypertension and cardiovascular diseases (CVD) and will consist of the adverse effects of hypertension, the importance of adhering to a medication schedule, non-pharmacological approaches for controlling hypertension and preventing CVD, advice on weight loss strategies, low salt and saturated fat intake in the diet and high consumption of fruits and vegetables, promoting physical activity, and smoking cessation. These sessions will be delivered face-to-face

by LHWs every three months. At the end of the HHE session, LHW will complete an HHE checklist with details on participants and put a checkmark against each of the areas listed above addressed during the HHE session, (Appendix: 6a English and 6b Sindhi). Our baseline team will visit to all known hypertensive individuals (known and newly diagnosed) and will obtain informed consent from each individual who wishes to participate in the study (Appendix 7a-English, 7b-Sindhi).

2. Training of physicians in blood-pressure monitoring, management of hypertension, and use of the checklist (Appendix: 9). The physicians will be trained in using a hypertension management manual and an algorithm that was developed in the earlier COBRA study and iterated based on physician feedback, drug availability in BHUs and the latest guidelines (Appendix: 10-1, 10-2, 10-3). The target blood pressure was a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg. Physicians will receive refresher training in 3 months and annually thereafter.
3. Designated hypertension triage counter and hypertension care coordinators in Basic Health Units. A functional hypertension triage counter will be established at the Basic Health Units enrolled in the study. This will facilitate the care of hypertensive individuals who present to the clinic with a GP referral checklist (Appendix: 5a English, 5b Sindhi). The counter will be equipped with a digital BP device for standardized measurement of BP by a trained clinic nurse/assistant before evaluation by a trained physician. Additionally, a hypertension care coordinator will be appointed at each government clinic to facilitate tracking referrals by the LHWs of individuals with poorly controlled BP.

*Implementation Strategies*

In addition to MCHI, the intervention arm will also receive implementation strategies. While the specific implementation strategies will only be defined at the end of Phase 1, we envisage that these will be grouped as follows:

1. Level 1 Strategies: Soon after receiving training on MCHI, the staff and facilities allocated to the intervention arm will be offered the first set of strategies. While important, these would be relatively easy to implement and may require a change in processes. These may include audits and feedback, the use of digital technology to set reminders and assist healthcare providers and identifying and supporting local champions.
2. Level 2 Strategies: These strategies would typically require changes in the infrastructure. For example, these may include offering medications, changing recording and reporting systems and providing clinical supervision. Due to the nature of changes required to implement these strategies, these are more likely to be less feasible but still important.
3. Level 3 Strategies: These would typically include financial strategies. For example, these may require financial restructuring to reward performance, financial incentives

for additional services or finding new ways to finance the intervention. Such strategies tend to be most challenging to implement but likely to be effective.

We will start with Level 1 strategies. Following interim analyses after the first and second follow-ups, respectively, the investigators will decide to either upgrade to the next level strategies or to continue at the current level using a set of pre-defined UPGRADE criteria, as follows:

| Criteria | Indicator | Source of data |
|---|---|---|
| Adoption | At least 80% of all participants in the intervention arm, received a home visit by LHW for HHE and BP monitoring | LHW checklist validated by the participant follow-up questionnaire |
| Implementation | At least 80% of all participants received advice either from the trained physicians at Basic Health Units or practicing in the community after being identified as having uncontrolled BP (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) by LHW at the first home visit | LHW and physicians' checklists validated by participant follow-up questionnaire |

If all of the above criteria are met, the current level of implementation strategies will continue. However, even if one of the criteria is not met, the implementation strategies will be upgraded to the next level.

**Outcomes and Data Collection**

Primary outcome

Primary outcome will be the change in number of BP-lowering medications per participant. After estimating the proportional change in the number between the baseline and the 24-month follow-up, the mean difference between the intervention and control arms will be estimated. A mean difference of 0.1 would be considered clinically significant.

*Implementation outcomes*

In addition, based on the RE-AIM Framework [21, 22], we will gather data on implementation outcomes for both the intervention and control arms (table 1).

**Table 1. implementation outcomes based on RE-AIM framework**

| RE-AIM domain | Outcome measure | Data source |
|---|---|---|
| Adoption | 1a. The proportion LHWs from 30 study clusters conducting HHE sessions, monitoring blood pressure and doing referrals of hypertensive patients to health facilities during first 12 months | -LHW HHE & referral checklist<br>-Baseline/follow up survey |
| | 2a. The proportion of Physicians from 30 study clusters diagnosing and providing hypertension management to hypertensive patients at BHU/RHC referred by LHW during first 12 months | -GP checklists<br>-Baseline/follow up survey |
| Implementation | 1b. The mean number of planned home visits/participant over 24 months (a maximum of eight visits, one every 3 months, are planned per participant) by LHW for HHE and BP monitoring | -LHW HHE & referral checklist<br>-Baseline/follow up survey |
| | 2b. The mean number of healthcare contacts with Physicians at the Basic Health Unit per participant over 24 months among those identified as having uncontrolled BP (SBP≥140 mm Hg &/or DBP≥90 mm Hg) by LHW at one or more than one occasion during the trial | -LHW HHE & referral checklist<br>-Baseline/follow up survey |
| Maintenance | 3a. The proportion of participants receiving visit by LHW for HHE and BP monitoring at 6, 12, 18 and 24 months. | -LHW HHE & referral checklist<br>-Baseline/follow up survey |

| | | |
|---|---|---|
| | 3b. The proportion of participants that received advice and/or treatment from the GPs at the Basic Health Unit after being identified as having uncontrolled BP (SBP≥140 mm Hg &/or DBP≥90 mm Hg) by LHW at 6, 12, and 24, months. | -GP checklists<br>-Baseline/follow up survey |

***Effectiveness outcome:***

- The proportion of participants with controlled blood-pressure (SBP <140 mmHg and DBP <90 mmHg)
- The participant reported health status according to the mean score on the visual-analogue scale of the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L; range, 0 to 100, with higher scores indicating better health). The HRQoL score based on responses to the EQ-5D-5L and public preferences will also be used.

**Secondary outcome**

- Mean systolic & diastolic blood pressure change from baseline to endline between intervention and control arms

**Data collection: baseline and follow-up surveys**

Data from the recruited study participants will be collected at baseline and then every six months via follow-up surveys over a period of two years. Each survey's duration will be 6 months. Each participant will have a follow-up done at an interval of 6 months with a 4-week +/- grace period those who may not be available at first visit. The data collection instrument, i.e., questionnaire will be transformed into an android mobile application and data will be collected digitally. All the field staff will be provided training for data collection and the use of android version of the questionnaire. Data will be collected on the variables including socio-demographics, medical and family history dietary patterns, tobacco consumption (smoking and smokeless tobacco), secondhand smoke exposure, alcohol consumption, physical activity levels, sleep, quality of life (using EQ-5D-5L), and health expenditure on CVD related medical conditions. In addition to blood pressure measurements, height, weight and waist circumference will also be measured. Biological measurements will be done at baseline and include fasting blood sugar, serum LDL, HDL, total cholesterol, and serum creatinine and 24 hour urinary sodium excretion (sub-sample of 200 participants, randomly selected individuals whose serum creatinine is normal)).

In addition to the above, data on the risk factors and high-risk behaviors for cardiovascular disease (CVD), quality of life and CVD treatment-related expenses will be collected through a structured questionnaire (Appendix: 8a English, and 8b Sindhi. The variables will cover the following domains:

- Socio-demographics
- Dietary patterns/habits
- Tobacco consumption (smoke and smokeless tobacco)
- Secondhand smoke exposure
- Alcohol consumption
- Physical activity levels
- Sleep
- Out-of-pocket healthcare expenses for CVD

The data collection instrument, i.e., questionnaire will be digitized into an android application. The questionnaire can then be opened on android phones and used to collect data in the field. All the field staff will be provided with training in data collection. They will be given password-protected access to android versions of baseline and follow-up questionnaires. Project team members will also have password-protected access to the data. Additional set of questions to measure study's zero time have also been added (Appendix 11).

In addition to the questionnaire, the following measurements will be carried out:

- Blood pressure
- Height, weight, and waist circumference
- Fasting sugar
- LDL, HDL, and total cholesterol
- Serum creatinine
- 24 hrs urinary sodium excretion (randomly selected 200 individuals whose serum creatinine is normal)

The biological samples will be collected early in the morning in a state of fasting. For this, members of the data collection team will visit study participants in the early morning, collect samples and transport these to the nearest AKU laboratory in the district.

A similar pattern will be followed for follow-up surveys. In case a participant is not available at the time of the visit, their availability will be sought on the telephone before paying them a second visit. Follow-up surveys will be conducted every 6 months to determine the frequency of risk factors over two years. Laboratory tests will be conducted at baseline only.

For the deaths reported among study participants during the study, verbal autopsy will be performed using WHO verbal autopsy questionnaire (2016). Study data will be shared with data safety & management board (DSMB) on a six-monthly basis. Data of hospitalizations collected during follow-up surveys will be reviewed by safety events review committee at AKU.

**Process Evaluations**

The fidelity of the implementation will be evaluated, and reasons for any differences between the observed and expected outcomes will be investigated. Process measures for the implementation strategies will be defined and included in the trial at the time of randomization. Additionally, the following process measures will be included:

The percentage of scheduled HHE sessions conducted at the household level (based on the HHE session checklist collected from LHWs).

The percentage of individuals with hypertension referred to a trained physician by LHWs (according to the physician referral checklist collected from hypertensive individuals).

- The percentage of individuals with hypertension assessed by a trained physician (as per the physician management checklists collected from the district health office).

**Sample size**

Each cluster is served by 1 BHU and 1-2 LHW on average. Each LHW serves a minimum of 100 households or 500 people (an average of 5 per household). Therefore, each cluster would have at least 2,500 people. Out of these, 625, would be above the age of 35 and of these 156 will have hypertension (25% prevalence of hypertension). If 20% refuse to participate, approximately 125 people will be eligible and ready for participation in each cluster.

We propose to assess, between the two arms, a mean difference of 0.15 in the change in the number of BP-lowering medications/participants between the baseline to the final follow-up. If the implementation strategies are effective, over and above MCHI, those with a higher score at baseline are expected to show a bigger difference than those with a low score. Assuming a mean difference of 0.15, a standard deviation of 0.83 (from the pooled data for Bangladesh and Pakistan, Jafar et al, 2020), 90% power, 5% alpha, correlation=0.5, ICC=0.02 (Jafar et al, 2020 - sample size) and average cluster size of 100, then we would need to randomize 30 clusters (3,000 participants).

## Phase 3: Barriers and Facilitators to Scale Up

Once intervention delivery is complete, the healthcare staff delivering MCHI including LHW and physicians will be asked to take part in Focus Group Discussions (FGD). There will be 4 Focus Groups (6-8 participants per FGD). Two will include LHWs from the intervention and control site respectively while the other two will include physicians from the two arms. In addition, we will also conduct in-depth qualitative interventions with managers including LHW district coordinators, and district health officers. Healthcare staff and service managers will be provided with information and asked to consent to participation (Appendix: 11). Each will focus on their experience of delivering and implementing the MCHI. In these FGDs and interviews, we will ask them about the CFIR barriers/drivers identified pre-intervention that were predicted to have the most potential to impact positively/negatively on intervention implementation (i.e., were these barriers/drivers evident in practice, were there other unanticipated barriers/drivers, and how supportive or not were the ERIC strategies.

All interviews and FGDs will be conducted in the local language, face-to-face using topic guides (Appendix: 12) and digitally audio-recorded after obtaining written consent from the participants. A hermeneutics approach, which encourages participants to discuss features of

the intervention to elicit data on their experience and evaluation of its delivery/receipt will be used.[15]

Interviews and FGDs will be transcribed verbatim and translated into English and analyzed using the Framework Approach[16] which is particularly useful for understanding and improving programmes/policies and when multiple researchers are working with the data.[17] Excel software will aid in data handling. Integration of qualitative and quantitative findings will be done using a 'triangulation protocol.'[18]

Two post-implementation workshops, one in each district, will help us use the actual barriers and drivers identified during the delivery of MCHI to refine implementation strategies. We will invite the same groups of stakeholders as in the pre-implementation workshops. Participants will be presented with the findings of the FGDs describing the actual barriers/drivers to delivering MCHI contrasting it with those considered as potential barriers/drivers during Phase 1. Participants will also learn about the extent to which the healthcare staff/service managers believe the respective implementation strategies succeeded in their execution. They will be allowed to re-endorse the list of the implementation strategies populated by using the CFIR-ERIC Mapping Tool,[13] before the workshop. They will be asked to select and rank up to 7 strategies that would best address each CFIR barrier/driver. As before, only those strategies will be selected for the final list which would be either at level 1 or level 2 for at least one CFIR barrier/driver. At the end of these workshops, we will have a list of barriers/drivers (CFIR constructs) to implementation and corresponding (ERIC) strategies to best support any future scale-up in the country.

**Statistical Analysis**

Analyses will be described in detail in a Statistical Analysis Plan drafted by the trial statisticians, agreed with the trial independent groups. Analyses will be conducted in accordance with the AKU's SOPs and will be undertaken in Stata v17 or later (to be confirmed in the final report). Significance tests will be two-sided at the 5% significance levels under the principles of intention-to-treat. Reporting will be in accordance with CONSORT guidelines for cluster RCTs.

The flow of clusters and participants through the trial will be presented in a CONSORT diagram. All baseline data will be summarized descriptively by treatment group. The primary analysis will compare the change in the number of medications/participant from the baseline to the last follow-up between groups. The primary outcome will be analyzed using a linear mixed model with fixed effects for baseline value of the outcome, district, distance of the cluster from the clinic, age, sex, time and interaction of time with a randomized group and random effects for the clusters and to account for the repeated measures by participants over time. The treatment effect at all time points will be extracted in the form of an adjusted mean difference, 95% confidence interval and p-value (with the primary being at 6 months). Continuous secondary outcomes will be similarly analyzed and other outcomes by appropriate regression techniques for the type of data.

**Economic Analysis**

A detailed Health Economic Analysis Plan will be developed by the study health economists. The cost-effectiveness of the implementation strategies will be assessed in terms of: i) their impact on improving its adoption, implementation and maintenance, and ii) their impact on patient health outcomes.

Costs will be assessed from a healthcare perspective, reflecting the costs of the implementation strategies, the intervention, wider healthcare resource use related to CVD and out-of-pocket payments. For their impact on adoption, implementation and maintenance, outcomes will include. Cost-effectiveness will be expressed as an incremental cost per unit of effect. For their impact on health, outcomes will include life years, quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs). Cost-effectiveness will be expressed as an incremental cost per unit of health outcome and incremental net health and monetary benefits based on accepted cost-effectiveness thresholds.

# Ethical Aspects

## Personal Data

The following personal data will be collected as part of the research:

Name, contact details, village name, participant/household address, household roster, marital status, ethnicity, gender, age, date of birth, ethnicity, educational level, and occupation. Personal data will be stored by the research team in a password-protected format. Only the project team will have access to the data. Personal data will be stored in digital format and retained for 7 years as per institutional policy. However, it will be anonymized, and no personal identifiers will be attached to it whenever referred to in a publication or a presentation.

## Ethical conduct

The study will be conducted in accordance with the principles of the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice (ICH GCP) in addition to the principles of the ethics committee(s)/Institutional Review Boards (IRBs) who have reviewed and approved this study. Before the study can commence, all required approvals will be obtained, and any conditions of approvals will be met.

## Consent

A member of the research team or project field team will approach the participants. Participants will be explained the purpose of the study and any queries raised will be satisfied. A separate place will be arranged for conducting interviews to maintain privacy and confidentiality.

## Confidentiality

The identity of participants in this study will be treated as confidential. The results of the study may be published for scientific purposes but will not give their name or include any identifiable reference. The data will be anonymized by assigning codes and personal identifiers will be removed. However, any records or data obtained as a result of participation in this study may be inspected by the sponsor or by AKU ERC members.

## Right to refuse or withdraw

Participants will be informed and explained that they are free to choose whether to participate in this study. There will be no penalty or loss of benefits to which they may be entitled otherwise if they choose not to participate. They'll be provided with any significant new findings developed during this study that may relate to or influence their willingness to continue participation. For participants who cannot read, a witness will be identified who will additionally ensure that the research that research participant has understood the consent. Such participants will be asked to provide a thumb impression on the consent form whereas the witness will sign on the consent form.

Participants can also be withdrawn by the primary investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from:

- All aspects of the study but continued use of data (and samples) collected up to that point.
- All aspects of the study with deletion of all previously collected data (and samples).

## Specific cultural considerations

The field team responsible for data collection will comprise of male and female members. Given the cultural context, it will be appropriate will appropriate to have a female team member interview the female participants wherever appropriate. In certain villages, the field team may require permission from the village elders before starting data collection. In that case, a meeting with village elders will be organized wherever appropriate to apprise them of study objectives and seek their permission.

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