Study Protocol

Community-based, eHealth supported management of cardio-vascular risk-factors by lay village health workers for people with controlled and uncontrolled arterial hypertension in rural Lesotho

Joint protocol for two cluster-randomized trials within the ComBaCaL cohort study (ComBaCaL aHT TwiC 1 & ComBaCaL aHT TwiC 2)

Type of Research Project	Research project involving collection of health-related data from persons

Study acronym/ID	ComBaCaL aHT TwiC 1 & aHT TwiC 2		
Protocol Version Nr	1.1	**Date**	07.02.2023
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1 GENERAL INFORMATION

1.1 List of Project Leaders and other key persons involved in the study

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The project leaders are qualified individuals by education and training and responsible for the whole project. All further key persons are also qualified by education and training to perform their assigned tasks and responsibilities.

1.2 Signatures

Study Title: "Community-based, eHealth supported management of cardiovascular risk factors by lay village health workers for people with controlled and uncontrolled arterial hypertension in rural Lesotho: Joint protocol for two cluster-randomized trials within the ComBaCaL cohort study (ComBaCaL aHT TwiC 1 & ComBaCaL aHT TwiC 2)"

The following project leaders have approved the protocol version 1.1, dated 07.02.2023, and confirm hereby to conduct the project according to the current version of the Declaration of Helsinki as well as all national legal requirements and guidelines as applicable.

Principal Investigators:

- I have read this protocol version 1.1, dated 07.02.2023, and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.
- I will ensure that all individuals and parties contributing to this study are qualified and I will implement procedures to ensure integrity of study tasks and data.
- I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed and trained regarding their activities within the study conduct.
- I will use only approved informed consent forms and will fulfil all responsibilities for submitting pertinent information to the Independent Ethics Committees responsible for this study.
- It is understood that this protocol will not be disclosed to others without prior written authorisation from the Project Leader or Sponsor, except where required by applicable local laws

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1.3 Abbreviations / Glossary of terms

AE	Adverse event
AESI	Adverse event of special interest
aHT	Arterial hypertension
BMI	Body mass index
BG	Blood glucose
BP	Blood pressure
CC-VHW	Chronic care village health worker
CC nurse	Chronic care nurse
cmRCT	Cohort multiple randomized controlled trials
ComBaCaL	Community-Based Chronic Disease Care Lesotho
CVD	Cardiovascular disease
CVDRF	Cardiovascular disease risk factor
DHMT	District Health Management Team
eCRF	Electronic case report form
EKNZ	Ethics Committee of Northern and Central Switzerland
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICHOM	International Consortium for Health Outcomes Measurement
IEC	Independent Ethics Committee
IT	Information technology
ITT	Intention-to-treat
LHW	Lay healthcare worker
LMICs	Low- and middle-income countries
MoH	Ministry of Health
NCD	Non-communicable disease
NHREC	National Health Research Ethics Council
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SPC	Single-pill combination
T2D	Type 2 diabetes mellitus
TwiC	Trial within cohort
VHW	Village health worker
WHO	World Health Organization

2 SYNOPSIS

Project Leaders	Prof. Dr. Niklaus Labhardt Dr. Dr. Alain Amstutz
Study Title	Community-based, eHealth supported management of cardiovascular risk factors by lay village health workers for people with controlled and uncontrolled arterial hypertension in rural Lesotho: Joint protocol for two cluster-randomized trials within the ComBaCaL cohort study (ComBaCaL aHT TwiC 1 & aHT TwiC 2)
Short Title/Study ID	ComBaCaL aHT TwiC 1 & aHT TwiC 2
Protocol Version and Date	Version 1.1, 07.02.2023
Study Category with Rationale	Implementation research trial Risk category A
Background and Rationale	Globally, arterial hypertension (aHT) is the single most important risk factor for early mortality, accounting for 10.8 million or almost 20% of all deaths in 2019[1]. Low- and middle-income countries (LMICs) are bearing a disproportionally high, still increasing share of the aHT-related burden, while many high-income countries have managed to reduce aHT-related burden substantially over the past decades.[1–4] Besides demographic changes and the increasing prevalence of lifestyle-related risk factors and resulting conditions, the inadequate health system response on preventive and therapeutic level is a major reason for the disproportionally high cardiovascular disease (CVD) burden in LMICs. In many LMICs health systems are poorly prepared to address the increasing burden caused by aHT and other non-communicable diseases (NCDs) resulting in massive treatment gaps, with only around 10% of people living with aHT in LMICs reaching treatment targets[5]. Effective, affordable, scalable setting-specific strategies are required for a reversal of this baleful trend. Increasing the global coverage of antihypertensive medications alone has been estimated to delay around 40 million deaths over 25 years[6]. The task-shifting from facility-based healthcare professionals to lay healthcare workers (LHWs) at community-level has been identified as a promising solution to increase access to aHT treatment in LMICs[7]. Many LMICs have established LHW systems focusing on maternal and neonatal health and on communicable diseases, especially HIV/AIDS. However, in recent years, increasing evidence has emerged showing a beneficial effect and high cost-effectiveness of LHW-based models on diseases outside of this traditional scope, especially for NCDs, such as aHT or type 2 diabetes mellitus (T2D). For aHT, most studies about LHW-led care models have focused on screening, counselling and referral interventions.[7–12] Independent of LHW involvement, sound evidence supports the use of simple aHT treatment protocols across different provider levels that include the prescription of single-pill combinations (SPCs) to reduce pill burden for patients and thereby promote adherence.[13] Current knowledge gaps include the question of whether prescription of first-line SPCs can be included safely and effectively in LHW-led aHT care models

	at community-level complementing the screening, counselling and referral services for which benefit has been shown already. Furthermore, evidence of whether and how community-based aHT care models could be adapted and successfully implemented in sub-Saharan Africa is very limited[14] as the recent landmark trials have been conducted in other parts of the world.[8,11,15] Building on this knowledge and addressing the mentioned gaps, we are planning to conduct a cluster-randomized intervention within the ComBaCaL (Community-Based Chronic disease care Lesotho) cohort study (EKNZ ID 2022-00058, NH-REC ID 210-2022, clinicaltrials.gov ID NCT05596773), a platform for the investigation of chronic diseases and their management in rural Lesotho that is maintained by local chronic care village health workers (CC-VHWs). CC-VHWs are lay healthcare workers operating within the Lesotho Ministry of Health (MoH) Village Health Worker Program who receive a specific training to deliver chronic care services. The here-described intervention has been developed based on a local NCD prevalence survey and burden assessment (NH-REC ID 130-2021), a scoping literature review[14], multiple workshops with different stakeholders in Lesotho and the ComBaCaL pilot cohort study (NH-REC ID 176-2021). In the intervention clusters, CC-VHWs operating within the existing healthcare system will be capacitated to screen for and diagnose aHT, to prescribe first-line antihypertensive SPCs for eligible participants and to monitor antihypertensive treatment supported by a tailored clinical decision support application (ComBaCaL app) in their villages. The control group consists of people diagnosed with aHT living in villages that are also part of the ComBaCaL cohort but not sampled for the intervention (control villages), where CC-VHWs will only screen for and diagnose aHT with subsequent standardized counselling and referral to the closest health facility if aHT is present, but no village-based prescriptions or treatment monitoring and support. We are planning to assess the effectiveness of this intervention in two different trial populations: On the one hand in people with uncomplicated but aHT and BP values above treatment target (≥ 140/90 mmHg) at baseline (aHT TwiC 1), and on the other hand in people with uncomplicated aHT and BP values below treatment target at baseline (aHT TwiC 2). We hypothesize that the ComBaCaL model of care is superior in ComBaCaL TwiC 1 and non-inferior in ComBaCaL TwiC 2. Randomization for the two TwiCs will be done at cluster level, meaning that all people with aHT in one village will be offered the same care package from their local CC-VHW.
Objectives	**Primary objective aHT TwiC 1** • To assess the effectiveness of offering community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants in people with uncontrolled aHT (newly diagnosed or receiving treatment without reaching treatment targets (≥140/90 mmHg)) in rural Lesotho **Primary objective aHT TwiC 2** • To assess the effectiveness of offering community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participant in people with controlled aHT (receiving treatment at baseline and reaching treatment targets (<140/90 mmHg)) in rural Lesotho

	Secondary objectives aHT TwiC 1 & aHT TwiC 2 • Key secondary objective: To assess the effect of CC-VHW led, eHealth supported aHT care on 10-year CVD risk using the WHO CVD risk prediction tool[16] • To assess the effect of CC-VHW led, eHealth supported counselling on CVD risk factors including body-mass index (BMI), abdominal circumference, blood lipid status, tobacco use, physical activity and dietary habits • To assess the safety of CC-VHW led, eHealth supported prescription of first-line antihypertensive SPCs for people with controlled / uncontrolled aHT • To assess the effect of CC-VHW led, eHealth supported prescription of first-line antihypertensive SPCs for people with controlled / uncontrolled aHT on linkage and engagement in care and on adherence to treatment
Hypotheses and estimands	**aHT TwiC 1** • Primary hypothesis: Community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants is *safe and superior* with regard to BP control rates after twelve months compared to facility-based aHT care in people living with *uncontrolled* aHT in rural Lesotho • Primary estimand: Difference in the proportion of participants with a documented measurement of controlled aHT (BP <140/90 mmHg) in the primary endpoint window (12 months after enrolment) between community-based, CC-VHW-led, eHealth supported aHT care versus facility-based aHT care, in non-pregnant adults with uncontrolled aHT (BP ≥140/90 mmHg at baseline), who did not experience a traumatic death and did not move out of their village, irrespective of the uptake of the intervention, aHT treatment, aHT treatment adherence and adverse events. **aHT TwiC 2** • Primary hypothesis: Community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants is *safe and non-inferior* with regard to BP control rates after twelve months compared to facility-based aHT care in people living with *controlled* aHT in rural Lesotho • Primary estimand: Difference in the proportion of participants with a documented measurement of controlled aHT (BP <140/90 mmHg) in the primary endpoint window (12 months after enrolment) between community-based, CC-VHW-led, eHealth supported aHT care versus facility-based aHT care, in non-pregnant adults with controlled aHT (BP <140/90 mmHg at baseline), who did not experience a traumatic death and did not move out of their village, irrespective of the uptake of the intervention, aHT treatment, aHT treatment adherence and adverse events.
Endpoints	**Primary endpoint aHT TwiC 1 & aHT TwiC 2** • Proportion of participants whose blood pressure (BP) is within target (<140/90 mmHg) twelve months after enrolment

	Secondary endpoints aHT TwiC 1 & aHT TwiC 2 • Key secondary endpoint: 10-year CVD risk estimated using the WHO CVD risk prediction tool[16,17] six and twelve months after enrolment • CVD risk factors, such as smoking status, BMI, abdominal circumference, blood lipid status, dietary habits and physical activity six and twelve months after enrolment • Proportion of participants whose BP is within target (<140/90mmHg) six months after enrolment • Mean systolic (SBP) and diastolic (DBP) BP six and twelve months after enrolment • Linkage to care: proportion of participants not taking treatment at enrolment who have initiated pharmacological antihypertensive treatment six and twelve months after enrolment • Engagement in care: proportion of participants who are engaged in care, defined as reporting intake of antihypertensive medication as per prescription of a healthcare provider (CC-VHW or healthcare professional) six and twelve months after enrolment or reaching treatment targets without intake of medication • Self-reported adherence to antihypertensive medication and lifestyle advices • Occurrence of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) within six and twelve months after enrolment
Intervention	CC-VHWs are providing screening, diagnosis, first-line antihypertensive treatment for eligible participants and treatment monitoring and support at community-level. CC-VHWs are equipped with a tablet where a dedicated application, the ComBaCaL app, guides them to provide first-line antihypertensive SPCs to eligible individuals and treatment monitoring and support to all individuals found to have aHT. In addition, the CC-VHW offers enhanced lifestyle counselling, lipid-lowering treatment (statin) to participants with a high CVD risk and antiplatelet treatment (aspirin) to participants with a history of stroke or myocardial infarction. Appropriately trained, supervised and mentored by chronic care nurses (CC nurses) and guided by the ComBaCaL app they will follow-up persons with aHT to monitor adherence, life-style changes, treatment response and side-effects.
Control	Control villages will follow the standard of care in the ComBaCaL cohort study. CC-VHWs will also receive tablets with the ComBaCaL app installed. They are trained, supervised and equipped to screen and diagnose aHT with subsequent referral to facility-based follow-up and care. In control villages the ComBaCaL app supports clinical decision making and documentation for screening, diagnosis and referral, but not prescription/provision of antihypertensive or lipid-lowering medication.
Study Design	ComBaCaL aHT TwiC 1 and aHT TwiC 2 are two cluster-randomized controlled trials that are identical in intervention, design and endpoints. They only differ in the trial population and trial hypothesis. TwiC 1 enrols individuals with uncomplicated aHT with baseline BP values above treatment targets and the hypothesis is that in intervention clusters where community-based treatment is offered, a higher proportion will have controlled aHT at twelve months' follow-up as compared to control clusters where participants are referred to the facility for further care after diagnosis. TwiC 2 enrols individuals with uncomplicated pharmacologically controlled aHT with the hypothesis that the

	offer of community-based antihypertensive treatment is non-inferior to facility-based care with regard to BP control rates at twelve months. The trials are nested within the ComBaCaL cohort study following a cohort multiple RCT (cmRCT) or trial within cohort (TwiC) approach[18,19]. 50% of the villages being part of the overarching ComBaCaL cohort will be randomly allocated to receive the TwiC intervention. The non-selected villages will serve as comparators and follow the regular ComBaCaL cohort activities conducted by CC-VHWs, including screening, diagnosis, standardized counselling and referral to a health facility for further therapeutic management. The TwiC intervention will be offered to all eligible people living with aHT in the sampled intervention villages. Individuals with uncomplicated uncontrolled and uncomplicated controlled aHT at baseline will be enrolled in aHT TwiC 1 and aHT 2 respectively.
Eligibility criteria	The two trial populations are mutually exclusive and together constitute the overall intervention population, thus every intervention-eligible participant is either allocated to aHT TwiC 1 or 2. **Inclusion criteria aHT TwiC 1** - Participant of the ComBaCaL cohort study (signed informed consent available) - Aged 18 years or above - Living with aHT, defined as reporting intake of antihypertensive medication or being newly diagnosed during screening via standardized diagnostic algorithm (see appendix of the "ComBaCaL cohort study protocol") - BP ≥140/90 mmHg at baseline **Inclusion criteria aHT TwiC 2** - Participant of the ComBaCaL cohort study (signed informed consent available) - Aged 18 years or above - Reporting intake of antihypertensive medication - BP<140/90 mmHg at baseline **Exclusion criteria aHT TwiC 1&2** - Reported pregnancy (at baseline or during follow-up)
Measurements and Procedures	For both TwiCs, screening, enrolment and baseline assessments will be conducted by CC-VHWs at community-level. We refer to the current version the "ComBaCaL cohort study protocol" for detailed information about the cohort set-up and procedures. In brief, CC-VHWs screen for and diagnose aHT using automated BP machines, based on standardized algorithms encoded in the tablet-based ComBaCaL app. In villages not allocated to the TwiC intervention (control villages), participants diagnosed with aHT receive a standardized counselling by the CC-VHW and are referred to the closest health facility for initiation or continuation of antihypertensive treatment. In the randomly selected intervention villages, eligible participants diagnosed with aHT will be offered pharmacological first-line treatment and all participants will be offered lifestyle counselling and treatment monitoring and support in the villages by CC-VHWs guided by the ComBaCaL app. Participants are free to accept or refuse the services offered by the CC-VHW at any time. In case of refusal of the aHT care at village-level, participants will be referred to the closest health facility for further care.

	Prior to the implementation, CC-VHWs in intervention villages will receive trainings on the basic mechanisms of action, cardiovascular risk reduction potential, contraindications and potential side effects of the antihypertensive SPC prescribed as well as on adherence counselling techniques, on the interpretation of BP values and on basic clinical examination skills for the recognition of possible adverse events. Direct guidance for treatment initiation, drug prescription, counselling and monitoring will be provided via the ComBaCaL app. All activities conducted by CC-VHWs in the communities, including counselling and drug prescription, will also be captured in the ComBaCaL app. Health care professionals and supervising study staff will monitor all activities in a web version of the app and will be intervening in case of missing data, non-adherence to the clinical algorithms, or unclear clinical conditions. The CC-VHWs may always request support by supervising health care professionals. In case of complicated disease, unclear diagnosis, or presence of clinical alarm signs or symptoms, participants will be referred immediately to the closest health facility for further investigation. Endpoint assessments after six and twelve months including BP and blood lipid status measurements, capturing of possible SAEs and AESIs as well as administration of questionnaires on adherence and modifiable CVDRFs will be conducted by CC-VHWs in an identical manner in intervention and control villages and captured in the ComBaCaL app. In addition, questionnaires about participants' satisfaction and acceptability of the TwiC intervention will be administered and semi structured interviews with a selection of participants, CC-VHWs and involved health care professionals will be conducted to qualitatively explore perceived risks, benefits and problems of community-based prescription of antihypertensive first-line SPCs.
Number of Participants with Rationale and Power Analysis	The ComBaCaL cohort will consist of inhabitants of around 100 (range 90-112) randomly selected villages in rural Lesotho. The estimated mean number of adult ComBaCaL participants per village is 100 resulting in an estimated 10'000 adult cohort participants. Sample size is calculated assuming an individual randomization inflated by a design effect that account for variation at cluster level, according to the code developed by Rotondi and Donner[20]. Based on preliminary results from an NCD prevalence survey in the region (NH-REC ID 139-2021), we expect the prevalence of aHT in the adult population in the rural setting in Lesotho to be around 18% with a control rate of 55%. Hence, considering an average cluster size of 100 adult inhabitants, the mean number of inhabitants with aHT is estimated at 18 (10 being controlled and 8 uncontrolled) with a standard deviation of 5. **aHT TwiC 1 superiority trial** In the intervention group, we assume an uptake of the care offered by CC-VHWs of 75% and a probability of success of 60% among individuals that accept community-based care and 30% among those that refuse community-based care. Hence, we estimate an overall success rate in the intervention group of 52.5%. We further assume an intra-cluster correlation of 0.015, a mean cluster size of 8 (standard deviation=5) and a probability of success of 35% in the control group. We calculate that a sample size of 304 (152 in each arm, 19 clusters per study arm) is required to detect superiority with a type I error of 0.025 and a statistical power of 80%.

	aHT TwiC 2 non-inferiority trial We set the non-inferiority margin for the odds ratio (OR) of reaching the primary endpoint to 0.58. On an absolute scale, this margin corresponds to a higher probability of failing to reach the primary outcome of 10 % in the intervention compared to the control group, assuming that the probability of success for the participants enrolled in the control arm is 80%. We assume an intra-cluster correlation of 0.015, a mean cluster size of 10 (standard deviation=5) and a probability of success of 80% in both intervention and control groups. This implies a sample size of 780 across 78 clusters (390 in each arm, 39 clusters per study arm) to be able to detect non-inferiority with a type I error of 0.025 and a statistical power of 80%. We inflate the calculated maximal number of cluster among the two TwiCs by 25% in order to account for uncertainties in the estimates of aHT prevalence, number of ComBaCaL village inhabitants and the consent rate. We finally aim to recruit 100 clusters (50 per study arm) for a total of 800 participants with uncontrolled aHT (TwiC 1) and 1000 participants with controlled aHT (TwiC2).
Study Duration and Schedule	The follow-up period for the TwiC is twelve months. We plan to enrol first participants in April 2023 and expect an enrolment period of around four months. Thus, the primary endpoint assessment for the last participants is planned for August 2024.
Study Centre(s)	Scientific project lead: Division of Clinical Epidemiology, University of Basel Implementation lead: SolidarMed Lesotho Study sites: 100 (90 to 112) villages in rural areas of Butha-Buthe and Mokhothlong districts in Lesotho
Statistical Analysis	Villages are our unit of random selection and individuals the unit of analysis. The primary analysis for both TwiCs will be the comparison of treatment control rates between the two study arms. Baseline characteristics will be described by study arm with summary statistics such as median and interquartile range or number and percentage. We will use a mixed effect logistic regression model with random intercept at the level of the clusters to assess the effect of the intervention. **Primary analysis aHT TwiC 1** Superiority will be assessed in an intention-to-treat (ITT) approach according to the 95% confidence interval of the odds ratio. **Primary analysis aHT TwiC 2** Non-inferiority will be assessed according to the 95% confidence interval of the odds ratio and the pre-defined non-inferiority margin in the ITT and the per-protocol (PP) set. Further details will be provided in the statistical analysis plan (SAP). **Secondary analysis aHT TwiC 1&2** Secondary endpoints will be reported using descriptive statistics such as mean and 95% Wald confidence intervals, frequency and percentages. Further details will be outlined in the SAP.
Ethical consideration	This project will be carried out in accordance with the research plan outlined in this protocol and with principles enunciated in the current version of the Declaration of Helsinki as well as all national legal requirements and guidelines as applicable. This protocol will be reviewed by the Ethikkommission Nordwest- und Zentralschweiz (EKNZ, Ethics Committee of Northern and Central Switzerland)

	by the National Health Research Ethics Committee (NHREC) of Lesotho before starting the study. Participation in the ComBaCaL cohort study and the TwiC intervention are voluntary and consent for both or the TwiC intervention alone can be withdrawn at any time. Potential risks associated with study participation include inadequate management by lay CC-VHWs. We will minimize this risk by providing adequate training, continuous supervision by health care professionals, and close guidance through the ComBaCaL eHealth application. Community-based care delivery is widely implemented in HIV care in Lesotho providing substantial benefits compared to purely clinic-based care. The here-presented intervention has the potential to increase the quality of care for aHT by improving access to treatment, increasing adherence and providing closer monitoring. The evidence generated in this study aims at informing future national and international clinical guidelines to improve chronic disease care in low-resource settings. Additionally, the community-based activities of the ComBaCaL project provide the added benefit of building a healthy and friendly community environment through community advocacy and participation, and helping to raise awareness and knowledge of chronic diseases within villages in Lesotho. Thus, the intervention is likely to have a direct positive impact on health outcomes of participants as well as generating evidence to improve context-specific NCD care delivery on a longer perspective.

3 BACKGROUND INFORMATION

3.1 Burden of arterial hypertension

Globally, arterial hypertension (aHT) is the single most important risk factor for early mortality, accounting for 10.8 million or almost 20% of all deaths in 2019[1]. Low- and middle-income countries (LMICs) are bearing a disproportionally high, still increasing share of the aHT-related burden, while many high-income countries have managed to reduce aHT-related burden substantially over the past decades.[1–4] In sub-Saharan Africa, the burden of non-communicable diseases (NCDs) has risen significantly over the past two decades, driven by the increasing prevalence of cardiovascular risk factors such as unhealthy diets, smoking, reduced physical activity, aHT, obesity, type 2 diabetes mellitus (T2D), dyslipidemia, and air pollution[3,21]. It is anticipated that NCDs will overtake communicable, maternal, neonatal, and nutritional diseases combined as the leading cause of mortality in sub-Saharan Africa by 2030[22]. Besides demographic changes and the increasing prevalence of lifestyle-related risk factors, the inadequate health system response on preventive and therapeutic level is a major reason for the disproportionally high cardiovascular disease (CVD) burden in LMICs. In many LMICs health systems are poorly prepared to address the increasingly prevalent NCDs including aHT, resulting in massive treatment gaps, with only around 10% of people living with aHT in LMICs having their condition well controlled[5]. Increasing the global coverage of antihypertensive medications alone has been estimated to delay around 40 million deaths over 25 years[6].

Lesotho is a landlocked country within South Africa, a typical example of an African LMIC where NCDs are overtaking HIV and other infectious diseases as major cause of disability, morbidity and early death[22]. A recent population-based survey in the districts of Mokhothlong and Butha-Buthe has revealed an aHT prevalence of 21% in the adult population in urban and rural areas combined and a relatively high treatment control rate of 40% compared to other LMICs (NH-REC 130-2021).

3.2 Decentralized healthcare delivery

Effective, affordable, scalable setting-specific strategies are required to reverse the trend of increasing NCD related burden in LMICs. The task-shifting to lay healthcare workers (LHWs) at community-level has been identified as a promising and cost-effective solution to increase access to aHT treatment in LMIC-settings[7–11,15]. Many LMICs have established LHW systems that may be capacitated to play a more active role in the management of NCDs[14]. Traditionally, most LHW systems focus on maternal and neonatal health and communicable diseases, especially HIV/AIDS[23–25], however in recent years, increasing evidence has emerged showing a beneficial effect and high cost-effectiveness of LHW-based models on diseases outside this traditional scope, especially for NCDs, such as aHT or T2D. For aHT, most studies about LHW-led care models have focused on screening, counselling and referral interventions, while knowledge about the effect of LHW-led prescription of antihypertensive medication is lacking.[7–12]

Independent of LHW involvement, sound evidence supports the use of simple treatment protocols across different provider levels that include the prescription of single-pill combinations (SPCs) to reduce pill burden for patients and thereby promote adherence.[13]

Current knowledge gaps include the question of whether prescription of first-line SPCs can be included safely and effectively in LHW-led aHT care models at community-level complementing the screening, counselling and referral services for which benefit has been shown already. Furthermore, evidence of whether and how community-based aHT care models could be adapted and successfully implemented in sub-Saharan Africa is very limited[14] as the recent landmark trials have been conducted in other parts of the world.[8,11,15]

Building on the existing knowledge and addressing the mentioned gaps, we are planning to conduct a cluster-randomized intervention within the ComBaCaL (Community-Based Chronic disease care Lesotho) cohort study (EKNZ ID AO_2022-00058, NH-REC ID 210-2022, clinicaltrials.gov ID NCT05596773), a platform for the investigation of chronic diseases and their management in rural Lesotho that is maintained by local lay chronic care village health workers (CC-VHWs). CC-VHWs are lay healthcare workers operating within the Lesotho Ministry of Health (MoH) Village Health Worker (VHW) program who receive a specific training to deliver chronic care services. As in many other sub-Saharan African

countries, the health system in Lesotho is facing the challenges of lacking human and financial resources. As a countermeasure, the integration of lay healthcare workers into the existing health system structures has been adopted many years ago[26]. Despite a drastic health workers shortage in Lesotho (0.9 doctors and 10.2 nurses per 10,000 inhabitants, particularly in the rural areas where the majority of the population lives (77.6%)[27], and the second-highest adult HIV prevalence globally (21.1%)[28], Lesotho has managed to reduce HIV transmission and AIDS-related deaths considerably. This success is based on decentralized HIV testing and care, involving lower cadre healthcare workers and lay VHWs to deliver accessible and equitable services for the urban and rural population alike. Currently the community-based health care delivery in Lesotho is focused on HIV and maternal and neonatal diseases, largely neglecting NCDs. Thus, NCD screening, diagnosis, management and prevention are located at the health facilities. However, due to high workload, staff shortages, lack of specific training, medication stock-outs and outdated guidelines, NCD services are often not delivered adequately at facility-level.

The Ministry of Health (MoH) of Lesotho has proposed in its NCD strategic plan that lessons learnt from HIV program should be incorporated into the NCD care and that delivery platforms should provide integrated HIV/NCD services.[29] Although various modelling studies from the region suggest that integrated service delivery can be cost-effective, robust evidence around community HIV/NCD delivery platforms and their key enablers is missing.[29, 30] To our knowledge, no studies have been conducted or policy documents developed on how to provide pragmatic and scalable prevention and treatment models for aHT or other NCDs in the context of a high communicable disease burden in Lesotho.

We plan to tackle the growing NCD pandemic through a multi-disciplinary research and implementation partnership, the Community-Based chronic disease Care Lesotho (ComBaCaL) program. ComBaCaL aims at establishing and validating a community-based care model focused on eHealth supported NCD service delivery by lay healthcare workers. The ComBaCaL cohort study provides the platform for the scientific assessment of the community-based NCD care model proposed.

In the here described trials within the cohort (TwiCs), we are aiming to specifically assess the effect of community-based aHT care including therapeutic management of uncomplicated aHT by lay CC-VHWs. The TwiC intervention has been developed based on a local NCD prevalence survey and burden assessment (NH-REC ID 130-2021), a scoping literature review[14], multiple workshops with different stakeholders in Lesotho and the ComBaCaL pilot cohort study (NH-REC ID 176-2021). In the intervention clusters, CC-VHWs operating within the existing healthcare system will be capacitated to screen for and diagnose aHT, to prescribe first-line antihypertensive SPCs to eligible participants and to monitor and support antihypertensive treatment supported by a tailored clinical decision support application (ComBaCaL app) in their villages. The control group consists of people diagnosed with aHT living in villages that are also part of the ComBaCaL cohort but not sampled for the intervention (control villages), where CC-VHWs will only screen for and diagnose aHT with subsequent standardized counselling and referral to the closest health facility if aHT is present, but no village-based prescriptions. We are planning to assess the effectiveness of this intervention in two different trial populations: On the one hand in people with uncontrolled aHT at baseline (aHT TwiC 1), and on the other hand in people with controlled aHT at baseline (aHT TwiC 2). We hypothesize that the intervention is superior in ComBaCaL TwiC 1 and non-inferior in ComBaCaL TwiC 2. Randomization for the two TwiCs will be done at cluster level, meaning that all people with aHT in one village will be offered the same care package from their local CC-VHW.

4 OBJECTIVES AND PURPOSE

4.1 Objectives

The overall objective of the ComBaCaL cohort study and nested TwiCs is to assess the impact of eHealth-supported, lay-led chronic disease control measures in rural Lesotho.
In the two aHT TwiCs, we will specifically assess the effect, safety and feasibility of community-based aHT care including therapeutic management of uncomplicated aHT by lay CC-VHWs in comparison to facility-based care after community-based screening and diagnosis.

4.1.1 Primary objective TwiC 1

- To assess the effectiveness of offering community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants in people with uncontrolled aHT (newly diagnosed or receiving treatment without reaching treatment targets (≥140/90 mmHg)) in rural Lesotho

4.1.2 Primary objective TwiC 2

- To assess the effectiveness of offering community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants in people with controlled aHT (receiving treatment at baseline and reaching treatment targets (<140/90 mmHg)) in rural Lesotho

4.1.3 Secondary objectives TwiC 1 & TwiC 2

- Key secondary objective: To assess the effect of CC-VHW led, eHealth supported aHT care on 10-year CVD risk using the WHO CVD risk assessment tool[16,17]
- To assess the effect of CC-VHW led, eHealth supported counselling on CVD risk factors including BMI, abdominal circumference, blood lipid status, tobacco use, physical activity and dietary habits
- To assess the safety of CC-VHW led, eHealth supported prescription of first-line antihypertensive SPCs for people with controlled / uncontrolled aHT
- To assess the effect of CC-VHW led, eHealth supported prescription of first-line antihypertensive SPCs for people with controlled / uncontrolled aHT on linkage and engagement in care and on adherence to treatment

4.1.4 Exploratory and implementation objectives TwiC 1 & TwiC 2

- To assess the effect of CC-CHW led aHT care on the number of eligible participants accessing lipid-lowering treatment
- To assess and describe implementation parameters, i.e. acceptance, uptake of and satisfaction with CC-VHW led, eHealth supported prescription of first-line antihypertensive SPCs for people with controlled/uncontrolled aHT among involved stakeholders
- To estimate the costs of CC-VHW led, eHealth supported prescription of first-line antihypertensive SPCs for people with controlled/uncontrolled aHT
- To assess quality indicators of the services provided and the data collected by CC-VHWs, such as completeness of the data collected and adherence to clinical algorithms provided via the eHealth application
- To assess the 10-year CVD risk using different risk assessment tools, such as the Framingham[31] and the Globorisk Score[32,33]
- To assess the effect of CC-VHW led, eHealth supported aHT care on quality of life using the EQ-5D-5L instrument[34] and on health beliefs using the Beliefs about Medicines Questionnaire (BMQ) adapted for people living with aHT[35,36]
- To assess the effect of CC-VHW led aHT care on the prevalence of BP values in the hypertensive urgency range (≥180/110mmHg)
- To assess the effect of CC-VHW led aHT care on self-reported access to care

4.2 Scientific justification of study population

The ComBaCaL cohort study will be located in rural villages of Butha-Buthe and Mokhothlong districts in Lesotho. Lesotho is a typical example of an African LMIC where a developing health system is facing the heavy double-burden of the still highly prevalent infectious diseases HIV/AIDS and TB in combination with a rapidly spreading NCD epidemic[22].

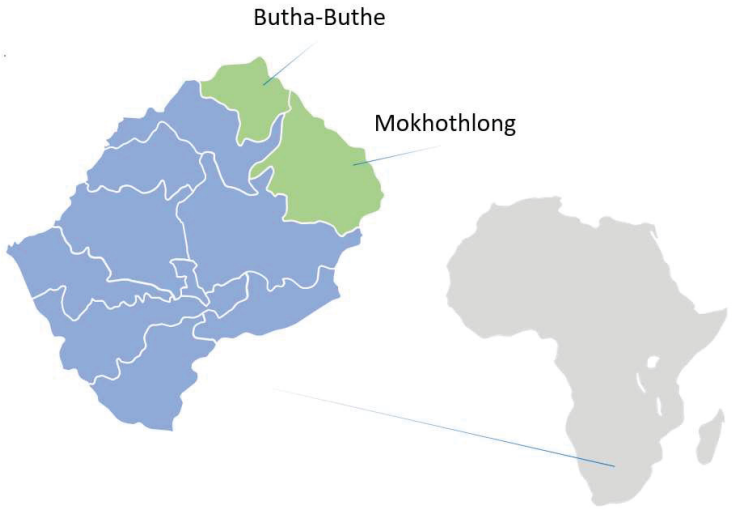

Figure 1 Map of Lesotho with the two districts Butha-Buthe and Mokhothlong

In the Lesotho health system, the VHW program plays a crucial role and has proven highly effective for the control of HIV/AIDS, especially for remote rural areas[26]. The Lesotho VHW program thus represents a meaningful starting point for implementation research on enhancing community-based intervention strategies and provides a setting that is representative for the health systems in many other LMICs, especially in sub-Saharan Africa, where lay worker led care has a similar standing.

5 HYPOTHESIS

5.1 Primary hypothesis TwiC 1 and primary estimand

Primary hypothesis: Community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants is safe and superior with regard to BP control rates after twelve months compared to facility-based aHT care in people living with uncontrolled aHT in rural Lesotho.

Primary estimand: Difference in the proportion of participants with a documented measurement of controlled aHT (BP <140/90 mmHg) in the primary endpoint window (12 months after enrolment) between community-based, CC-VHW-led, eHealth supported aHT care versus facility-based aHT care, in non-pregnant adults with uncontrolled aHT (BP ≥140/90 mmHg at baseline), who did not experience a traumatic death and did not move out of their village, irrespective of the uptake of the intervention, aHT treatment, aHT treatment adherence and adverse events.

5.2 Primary hypothesis TwiC 2 and primary estimand

Primary hypothesis: Community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants is safe and non-inferior with regard to BP control rates after twelve months compared to facility-based care in people living with controlled aHT in rural Lesotho.

Primary estimand: Difference in the proportion of participants with a documented measurement of controlled aHT (BP <140/90 mmHg) in the primary endpoint window (12 months after enrolment) between community-based, CC-VHW-led, eHealth supported aHT care versus facility-based aHT care, in non-pregnant adults with controlled aHT (BP <140/90 mmHg at baseline), who did not experience a traumatic death and did not move out of their village, irrespective of the uptake of the intervention, aHT treatment, aHT treatment adherence and adverse events.

6 STUDY DESIGN

6.1 Endpoints

For the endpoint assessments at twelve months, a range of 300 to 420 days after enrolment applies. For the endpoint assessments at six months, a range of 150 to 210 days applies.

6.1.1 Primary endpoint TwiC 1 & TwiC 2

- Proportion of participants whose blood pressure (BP) is within target (<140/90 mmHg) twelve months after enrolment

6.1.2 Secondary endpoints TwiC 1 & TwiC 2

- Key secondary endpoint: 10-year risk for a fatal or non-fatal CVD event estimated using the WHO CVD risk prediction tool[16,17] six and twelve months after enrolment
- CVD risk factors, such as BMI, abdominal circumference, blood lipid status, physical activity using the validated International Physical Activity Questionnaire Short Form (IPAQ-SF)[37] adapted to the local context and language according to the IPAQ recommendations[38], dietary habits using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa[39] and alcohol and tobacco use six and twelve months after enrolment
- Proportion of participants whose BP is within target (<140/90mmHg) six months after enrolment
- Mean systolic (SBP) and diastolic (DBP) BP six and twelve months after enrolment
- Occurrence of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) within six and twelve months after enrolment
- Linkage to care: proportion of participants not taking treatment at enrolment who have initiated pharmacological antihypertensive treatment six and twelve months after enrolment
- Engagement in care: proportion of participants who are engaged in care, defined as reporting intake of antihypertensive medication as per prescription of a healthcare provider (CC-VHW or healthcare professional) within the two weeks prior to assessment six and twelve months after enrolment or reaching treatment targets without intake of medication
- Self-reported adherence to treatment six and twelve months after enrolment

6.1.3 Exploratory endpoints and implementation indicators

- Number of consultations at a health facility and with the CC-VHW within six and twelve months after diagnosis
- Proportion of participants in the intervention clusters not taking up community-based drug treatment by CC-VHWs at baseline and proportion switching to facility-based care within six and twelve months Proportion of participants with aHT who stop drug treatment or interrupt drug treatment for more than three weeks or require a switch of drug treatment due to (perceived) adverse events (AEs) within six and twelve months after enrolment
- Proportion of participants who are reaching treatment targets (<140/90 mmHg) and are reporting no intake of antihypertensive medication in the two weeks prior to assessment after six and twelve months
- Proportion of high CVD risk participants eligible for lipid-lowering treatment who are accessing lipid-lowering medication six and twelve months after enrolment
- Participants', CC-VHWs' and involved health care professionals' perception of the risks, benefits and problems of community-based management of uncomplicated aHT by CC-VHWs
- Quality indicators of the CC-VHW activities, such as completeness of the data collected and adherence to clinical algorithms provided via the eHealth application
- Causes for the stop or interruption of treatment or switch to health facility-based treatment after initiation by CC-VHWs in the community
- Health system costs and individual costs for participants for the management of their condition within the first six and twelve months after diagnosis

- 10-year CVD risk estimated using the Framingham[31] and Globorisk[40] scores[33] six and twelve months after enrolment
- Quality of life using the EQ-5D-5L instrument[34]and health beliefs using the Beliefs about Medicines Questionnaire (BMQ) adapted for people living with aHT[35,36] after twelve months
- Access to care and access to medication using the questions as proposed by the International Consortium for Health Outcomes Measurement's (ICHOM) core outcome sets for aHT trials in LMICs[12] six and twelve months after enrolment
- Type and dosage of antihypertensive medications prescribed by CC-VHWs or healthcare professionals six and twelve months after enrolment
- Number of participants with BP in the hypertensive urgency range (180/110 mmHg) six and twelve months after enrolment

6.2 Measures to minimize bias

6.2.1 Blinding

Endpoint assessments will be conducted by the CC-VHWs; thus no blinding is possible.

6.2.2 Measurements

Baseline and endpoint assessments will be conducted by CC-VHWs supported by the ComBaCaL app. Protocols and instructions for correct BP measurements and sample collection as well as structured questionnaires for the assessment of lifestyle risk factors are provided in the ComBaCaL app. Details regarding the protocol for BP measurements can be found in the appendix of the current version of the "ComBaCaL cohort study protocol". All CC-VHWs will undergo a training with emphasis on correct BP measurements as well as interviewing techniques and data entry into the ComBaCaL app. For the duration of the study there will be regular field visits by supervising CC nurses to ensure that procedures for data collection are correctly followed by all involved CC-VHWs.

6.2.3 Randomization

50% of villages out of the ComBaCaL cohort villages will be randomly allocated to the intervention group by a statistician not involved in the study. The random allocation will be stratified by district (Butha-Buthe versus Mokhothlong) and access to health facility (easy versus difficult access, defined as needing to cross a mountain or river or travel >10 km to the nearest health facility).

6.3 Study duration and duration of participant's participation

The follow-up period for both TwiCs is twelve months. We plan to enrol first participants in April 2023 and expect an enrolment period of around four months. Thus, the endpoint assessment for the last participants is planned for August 2024.

6.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to NH-REC and EKNZ for approval before implementation while minor amendments will be submitted to NH-REC only.

6.5 Withdrawal and discontinuation

6.5.1 Individual level

Participants in the intervention villages may reject the intervention any time. They will be asked about the reasons for the rejection of village-based care, but may refuse to provide a reason for the rejection. The rejection of the intervention will not influence their affiliation to the ComBaCaL cohort study and their data will be included in the ITT analysis. Participants in the control villages who do not want their data to be included in the TwiC analysis need to withdraw the ComBaCaL cohort consent as agreeing to use of collected data as control data is an integral part of the ComBaCaL cohort consent.

As outlined in the "ComBaCaL cohort study protocol" all participants can withdraw cohort consent at any time. After withdrawal of cohort consent, the participant's profile in the ComBaCaL application will be de-activated and no further data will be collected. The possibility to re-enter the cohort later through contacting the local CC-VHW will be offered. Data collected until the time of withdrawal will be included in the analysis. By withdrawing the ComBaCaL cohort consent, automatically the intervention consent will be withdrawn, too.
The study team will not discontinue individual participants.

6.5.2 Study and cluster level

In intervention villages, the village chief may reject the intervention at village-level. The study team would then get in contact with the village chief to inquire the reasons for the intended rejection. If needed a community gathering ("Pitso") will be held. If after discussion between the village chief, the community and the study team, the request for rejection of the intervention persists, the intervention will be stopped in the village and all participants will be referred to the responsible health facility for continuation of treatment. ComBaCaL cohort activities without the intervention will continue in the village. Participants may be asked specifically about their perceptions of the rejection of the intervention at village-level.

If in a village, the CC-VHW is not able or willing to continue his/her tasks for the ComBaCaL study (i.e. due to death, migration, personal reasons, rejection by village chief or village population), the CC-VHW will be replaced while the village will remain in the study.

The Principal Investigators in consultation with Co-Investigators may choose to pause or discontinue the ComBaCaL cohort study in certain or all villages or to pause or discontinue the intervention in one or more intervention villages.
We refer to the "ComBaCaL cohort study protocol" for details regarding the criteria for interruption or stop of the ComBaCaL cohort study. If the ComBaCaL cohort is being interrupted or stopped in one or more villages, automatically also the nested TwiCs are interrupted or stopped in the concerned villages, while the participants will remain in the TwiC analysis population as outlined in section 10.

The reasons to pause or discontinue the TwiC intervention in all intervention villages include the following:

- Insufficient funding to continue the study
- Significant opposition by local health authorities
- Safety or other ethical concerns
- Alteration in accepted clinical practice, national policy or scientific evidence that make the continuation of the study unwise
- Insurmountable technical or organizational problems

The reasons to pause or discontinue the TwiC intervention in individual villages include the following:

- Significant opposition by local health authorities
- Safety or other ethical concerns
- Insurmountable organizational problems
- Impossibility to recruit a VHW from the village population in case replacement of the initially recruited VHW is required

The Principal Investigators would provide the project partners and the Co-Investigators written notice submitted at a reasonable time in advance of the intended discontinuation or pause of the ComBaCaL cohort study or the TwiC intervention. If the Principal Investigators choose to terminate or pause the ComBaCaL cohort study or the TwiC intervention for safety reasons, they will immediately notify all investigators and subsequently provide written instructions for study termination. Co-investigators may pause the ComBaCaL cohort study or the TwiC intervention in certain villages in case of safety concerns

without written notice in advance. If Co-Investigators wish to pause or discontinue the ComBaCaL cohort study or the TwiC intervention, they may address the request to pause or discontinue in written form to the Principal Investigators. Co-Investigators may not pause or discontinue the ComBaCaL cohort study or the TwiC intervention for other reasons than safety concerns without consulting the Principal Investigators.

6.6 End of trial

At the conclusion of the trial or premature termination, all study data will be locked and archived. The electronic database will be locked and a complete study dataset will be transferred to the statistician and the Principal Investigators through a secure channel. The study data will be stored by the Department of Clinical Research of the University Hospital Basel on a secure server for a minimum of 10 years and be destroyed thereafter (see section 11).
Participants in intervention and control villages will be informed about the results of the TwiCs through the CC-VHWs after the analysis is complete.

7 SELECTION OF STUDY PARTICIPANTS

7.1 Selection of villages

We refer to the "ComBaCaL cohort study protocol" for detailed information about the selection of villages for the ComBaCaL cohort.
Out of the ComBaCaL cohort villages, 50% will be randomly allocated to the intervention group. We refer to the paragraph 6.2.3 "Randomization" for information about the random allocation.

7.2 Recruitment of participants

We refer to the "ComBaCaL cohort study protocol" for details regarding the recruitment for the ComBaCaL cohort. For these TwiCs, CC-VHWs will screen for eligible individuals among adult ComBaCaL cohort participants in their villages via home visits.
The populations for the two TwiCs described in this protocol are mutually exclusive and together constitute the overall intervention-eligible population, thus every intervention-eligible participant is either allocated to ComBaCaL TwiC 1 or 2.

7.2.1 Inclusion criteria ComBaCaL-TwiC 1

- Participant of the ComBaCaL cohort study (signed informed consent available)
- Aged 18 years or above
- Living with aHT, defined as reporting intake of antihypertensive medication or being newly diagnosed during screening via standard diagnostic algorithm (see appendix of the "ComBaCaL cohort study protocol")
- BP ≥140/90 mmHg at baseline

7.2.2 Inclusion criteria ComBaCaL-TwiC 2

- Participant of the ComBaCaL cohort study (signed informed consent available)
- Aged 18 years or above
- Reporting intake of antihypertensive medication
- BP<140/90 mmHg at baseline

7.2.3 Exclusion criteria for both ComBaCaL-TwiC 1&2

- Reported pregnancy (at baseline or during follow-up)

Eligible participants in the intervention villages will be offered the intervention consisting of the prescription of first-line antihypertensive SPC for eligible participants, treatment monitoring and support, lifestyle counselling, lipid-lowering medication in case of high CVD risk and antiplatelet treatment for participants with a history of stroke or myocardial infarction by the CC-VHW after diagnosing aHT. Participants are free to accept or reject all or parts of the pharmacological and non-pharmacological care offered by the CC-VHW.
Data of ComBaCaL cohort participants living in villages not selected for the intervention will be used as "control arm". As per the ComBaCaL cohort study protocol and informed consent, no specific recruitment or participant information will be provided to the participants in control villages.

8 STUDY PROCEDURES

8.1 General Setting

Screening and enrolment for these TwiCs will be embedded into the regular ComBaCaL cohort activities conducted in the villages by CC-VHWs. We refer to the current version the "ComBaCaL cohort study protocol" for detailed information about the cohort set-up. At every participant encounter, the CC-VHW will screen for warning signs and symptoms (i.e. shortness of breath, severe headache, chest pain, new-onset confusion, impaired consciousness, severely impaired general state of health) and refer participants to the closest health centre in case of presence of any alarm sign or symptom.

8.2 Screening

Screening and diagnosis for aHT among the ComBaCaL cohort members will be conducted by CC-VHWs according to the algorithms provided in the appendix of the "ComBaCaL cohort study protocol". These algorithms are being encoded into the ComBaCaL app, guiding the question logic for data collection and serving as clinical decision aid for the CC-VHWs. After diagnosis of aHT, CC-VHWs will screen for the other eligibility criteria and based on the screening information, the trial eligibility will be determined via the ComBaCaL app.

8.3 Enrolment

ComBaCaL cohort participants meeting the eligibility criteria for one of the two TwiCs, will automatically be included in the respective TwiC population. We refer to the current version of the "ComBaCaL cohort study protocol" and to the section 13.3 of this document for details regarding the consent procedures. Participants in intervention villages may reject any component of the care offered any time during the study and request referral to a health facility for the continuation of their treatment. Participants consenting to participation but subsequently rejecting care offered by the CC-VHW might be approached for qualitative inquiry on the reasons for the refusal of community-based care.

8.4 Baseline

Most baseline data to describe the TwiC participants will be collected as part of the ComBaCaL cohort assessments (see current version of the "ComBaCaL cohort study protocol" for details). In brief, the following data will be collected by the CC-VHW at cohort baseline using the ComBaCaL eHealth application: age, sex, height, weight, abdominal circumference, household position, socioeconomic indicators of the household, level of education, income-generating activity, targeted medical history including previous aHT diagnosis, intake of antihypertensive medication, HIV status and cardiovascular complications, physical activity using the validated International Physical Activity Questionnaire Short Form (IPAQ-SF)[37] adapted to the local context and language according to the IPAQ recommendations[38], dietary habits using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa[39], self-reported alcohol and tobacco use, Participants aged 40 years or more or having a BMI above 25kg/m^2 will be screened for T2D using capillary blood glucose measurements.

In addition to the data collected as part of regular ComBaCaL cohort activities, further baseline information will be collected for TwiC participants based on the International Consortium for Health Outcomes Measurements' (ICHOM) outcome sets for aHT trials in LMICs[12]. Data collected at TwiC baseline include blood lipid status, quality of life using the EQ-5D-5L instrument[34] and health beliefs using the Beliefs about Medicines Questionnaire (BMQ) adapted for people living with aHT will be assessed[35,36].

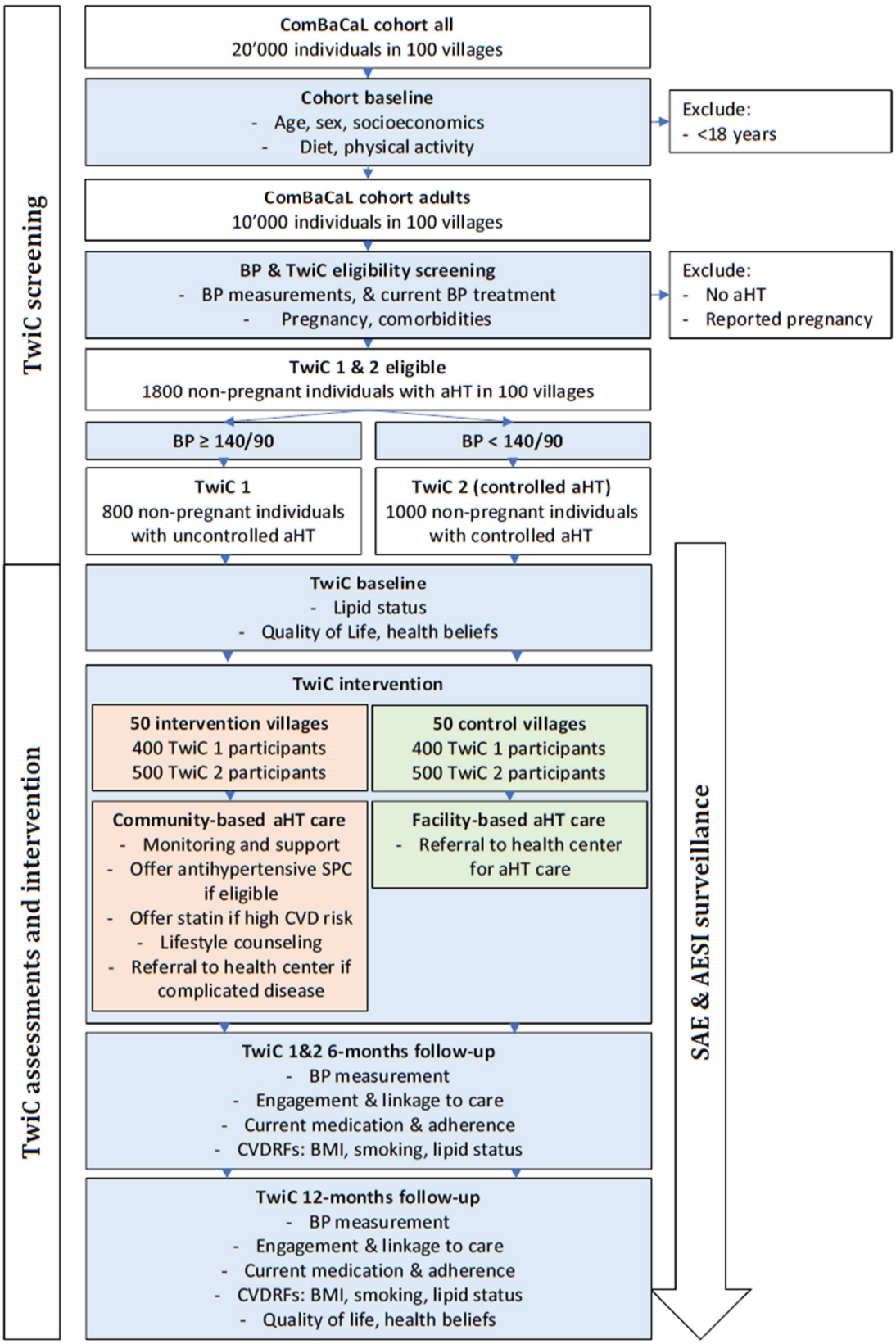

Figure 2 Flow of events. BP: blood pressure, aHT: arterial hypertension, TwiC: trial within cohort, SAE: serious adverse event, AESI: adverse event of special interest, CVDRFs: cardiovascular disease risk factors, BMI: body-mass index.

8.5 Intervention

In the intervention villages, CC-VHWs will offer a community-based aHT care package including pharmacological and non-pharmacological treatment and monitoring according to clinical algorithms based on international guidelines for primary healthcare level management of aHT[41,42] and the then effective Lesotho Standard Treatment Guidelines (under review at the time of submission of this protocol). Eligible participants will be offered antihypertensive first-line SPC and regular lifestyle counselling focussed on smoking cessation, healthy diet and regular physical activity. Participants with a high CVD risk and no contraindications will be offered lipid-lowering treatment. High CVD risk among the participants who all have aHT is defined as additionally having a history of stroke or myocardial infarction, having DM or chronic kidney disease (CKD) or being 50 years or older and having one or both of the following risk factors: BMI ≥ 30 kg/m^2, current smoking. Participants with a history of stroke or myocardial infarction and no contraindication will be offered antiplatelet treatment.

The CC-VHWs in the intervention villages will receive specific training focused on lifestyle counselling, drug prescription, screening for potential adverse events of drugs administered, and disease monitoring and dose adjustment after treatment initiation.

Direct guidance for treatment initiation, drug prescription, counselling and monitoring will be provided via the ComBaCaL app. All activities conducted by CC-VHWs in the communities, including counselling and drug prescription, will be captured in the application.

Health care professionals and supervising study staff will monitor all activities in a web version of the app and will be intervening in case of missing data, non-adherence to the clinical algorithms, or unclear clinical conditions. The CC-VHWs may always request support by supervising health care professionals.

In case of complicated disease (i.e. if treatment targets are not reached under first-line SPC), unclear diagnosis, relevant comorbidities or presence of clinical alarm signs or symptoms, participants will be referred to the closest health facility for further investigation. Participants are free to accept or refuse the treatment offered by the CC-VHWs. Participants refusing the CC-CHW-led treatment will be asked about the reasons for the refusal and will be referred to the responsible health facility for further management.

In control villages, CC-VHWs will refer participants to the responsible health facility for therapeutic management after enrolment and baseline assessment.

8.6 Follow-up and endpoint assessment

8.6.1 Scheduled follow-up visits and endpoint assessments

Follow-up visits by CC-VHWs including endpoint assessments will be scheduled six months (range 150 to 240 days) and twelve months (300 to 420 days) after TwiC enrolment.

During the follow-up visits, BP measurements will be conducted together with the collection of secondary endpoint data such as CVDRFs (physical activity, diet, blood lipid status, tobacco and alcohol use using the same assessment tools as for the baseline, height, weight, BMI, abdominal circumference), engagement in and adherence to antihypertensive treatment, quality of life and health beliefs.

During follow-up visits, CC-VHWs will inquire about relevant clinical events since the previous visit (including screening of the Bukana for documentation of respective events). These events will be documented in a dedicated electronic case report form within the ComBaCaL app. Safety outcomes of this TwiC (SAEs and AESIs, see section 9 for definitions) are a subset of the clinically relevant events that are captured as part of the ComBaCaL cohort study. All reports of SAEs and possible AESIs will be reviewed by the study physician for final assessment and classification.

In addition, specific questionnaires about participants' satisfaction and acceptability of the TwiC intervention will be administered and semi structured interviews with a selection of participants, CC-VHWs and involved health care professionals will be conducted to qualitatively explore perceived risks, benefits and problems of community-based therapeutic management of uncomplicated aHT. We will evaluate the quality of services provided and the data collected in the villages by analysing aggregated data and metadata of the reports submitted by the CC-VHWs via the eHealth application.

8.6.2 Clinical follow-up

In intervention villages, the CC-VHWs will conduct clinical follow-up visits according to the clinical algorithms provided via the ComBaCaL app. During these clinical follow-up visits, CC-VHWs will check BP values, monitor treatment adherence, check for treatment side effects, adjust treatment dose if required, provide lifestyle counselling and refer participants to the responsible health facility, if BP treatment targets are not met under high-dose first-line SPC or in case of side effects, clinical alarms signs or symptoms or relevant comorbidities. The therapeutic management provided by the CC-VHWs under guidance of the ComBaCaL app is in line with international guidelines on the treatment of aHT at primary healthcare level.[41,42]

In intervention and control villages, CC-VHWs will document deaths, hospitalizations and other relevant clinical events at any time after becoming aware of the event independent of scheduled visits. Likewise, if participants are moving out of the village, the CC-VHWs will document this in a dedicated form in the ComBaCaL app.

8.7 Schedule of events

	Cohort baseline	TwiC screening & baseline	Intervention follow-ups[1]	6-month follow-up	12-month follow-up
Time in days relative to TwiC enrolment	**-60 – 0**	**0**	**0 – 400**	**150 – 240**	**300 – 420**
ComBaCaL cohort informed consent	x				
Date of birth	x				
Height, weight, abdominal circumference	x			x	x
Sociodemographic data	x				
Short medical history[2]	x				
CVDRFs[3]	x			x	x
BG measurement	x			x	x
BP measurement		x	x	x	x
Health beliefs[4]		x		x	x
Quality of life[5]		x		x	x
Blood lipid status (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)		x		x	x
aHT specific medical history		x		x	x
Linkage to & engagement in care				x	x
Adherence to antihypertensive medication		x	x	x	x
Acceptability & satisfaction with aHT care[6]				x	x
Screening for relevant clinical events	x	x	x	x	x
Screening for clinical alarm signs/symptoms	x	x	x	x	x
TwiC Control					
Referral to health facility[7]		x		x	x
TwiC Intervention					
Offer SPC and treatment monitoring		x	x	x	x
Offer lipid-lowering treatment[8]		x	x	x	x
Lifestyle counselling		x	x	x	x
Referral to health facility[9]		(x)	(x)	(x)	(x)

1) Only for TwiC participants in intervention villages
2) Including personal and family history for aHT / DM and other relevant conditions
3) Physical activity using IPAQ-SF[37], dietary habits[39], tobacco and alcohol use
4) Using the Beliefs about Medicines Questionnaire[35,36]
5) Using the EQ-5D-5L instrument[34]
6) Only for a subset of participants
7) For initiation or continuation of aHT treatment and/or in case of clinical alarm signs or symptoms
8) Only to participants with high CVD risk
9) Only in case of clinical alarm signs or symptoms, participants refusing community-based aHT care, complicated disease, unclear diagnosis or relevant comorbidity

9 SAFETY CONSIDERATIONS

9.1 Definition and documentation of safety outcomes

Adverse event (AE)	Any untoward medical occurrence in a study participant, including occurrences that are not necessarily caused by or related to the study procedures
Adverse event of special interest (AESI)	AE consistent with complication of aHT, such as: • Myocardial infarction • Stroke • Symptomatic heart failure • Chronic kidney disease AE probably related to intake of antihypertensive medication, such as: • Intolerance reaction against antihypertensive medication leading to discontinuation of the medication concerned (including allergic reactions, drug interactions or rare severe side effects)
Serious adverse event (SAE)	Any AE that: • Results in death • Is life-threatening • Requires hospitalization or prolongation of existing hospitalization ○ Hospitalizations due to uncomplicated delivery are not considered as SAE • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect
Serious adverse event of special interest (SAESI)	SAE consistent with complication of aHT, such as: • Myocardial infarction • Stroke • Symptomatic heart failure • Chronic kidney disease SAE probably related to intake of antihypertensive or antidiabetic medication, such as: • Intolerance reaction against antihypertensive medication leading to discontinuation of the medication concerned (including allergic reactions, drug interactions or rare severe side effects)

CC-VHWs will be trained to screen for and to recognize adverse events of special interest (AESIs) and serious adverse events (SAEs) and to document them in the dedicated report form in the ComBaCaL app. AESIs and SAEs for this TwiC are a subset of the clinically relevant captured as part of routine ComBaCaL cohort activities

CC-VHWs may solicit AESIs and SAEs as part of the ComBaCaL activities in the following ways:

- Active reporting by participants or friends or relatives outside of scheduled CC-VHW visits (scheduled visits are defined as visits being triggered through the ComBaCaL app based on regular or clinical follow-up algorithms or visits being assigned by supervising healthcare professionals)

- Passive reporting by participants or friends or relatives after inquiry by CC-VHWs during scheduled VHW visits
- Clinical observation of CC-VHWs during or outside scheduled CC-VHW visit
- Screening of participants' Bukanas (personal health booklet)
- Reporting by health centre nurses

In intervention villages, additional visits are scheduled for the therapeutic management of aHT during which CC-VHWs will conduct additional AE screening including specific screening for AEs possibly related to the therapeutic intervention. The intervention-specific AE screening will be closely guided via the eHealth application (i.e. a list of symptoms to be inquired for each drug will be provided).

The anonymized, AESI reports will be submitted on a monthly basis to the study physician who will remain blinded to the village, CC-VHW or CC nurse related to the report submission. The study physician will classify the AESI reports of TwiC participants as SAEs (including type and if possible cause of SAE), AESIs (including type and if possible cause of AESI) or none of the two if sufficient clinical information for classification is available. If the clinical information available is not sufficient for classification of the case, the study physician will request the study Data Manager to unblind the respective report and then contact the responsible CC nurse and/or CC-VHW and ask for collection of further data.

9.2 Causality of SAEs and AESIs

A causality assessment of all SAEs and of AESIs possibly related to the therapeutic management of aHT will be performed by the study physician based on the reports submitted by the CC-VHWs. As a result of the causality assessment, the study physician will provide a statement whether the SAE/AESI is possibly, likely or definitely related or unrelated to the aHT care provided.

9.3 Management of AEs

9.3.1 Control villages

In control villages the entire clinical management after screening and diagnosis will be provided by healthcare professionals at the responsible health centre without direct influence by study staff. ComBaCaL study staff will provide capacity building in NCD management at all involved health centres and support in case of clinical questions. If CC-VHWs become aware of clinical events in their village during the follow-up period, they will refer the respective individual to the health centre.

9.3.2 Intervention villages

In intervention villages, mild, common side effects of the drugs administered, for which neither professional assessment nor other measures than observation or an interruption of the prescribed drug is required, will be managed by the CC-VHWs at community-level. For the assessment and management of these events, close guidance will be provided via the eHealth application. Additionally, CC-VHWs will have the possibility to seek clinical advice from the supervising health centre nurses or the CC nurses, either via messages sent through the eHealth application or via phone calls or field visits.
Any AEs going beyond mild, common side effects or any unclear clinical conditions will prompt referral to the responsible health facility for further assessment and professional management. The ComBaCaL study staff will not directly intervene in the management of such cases but provide clinical support to the health centre staff if required. Besides clinical support for the management of complex cases, the ComBaCaL study team will provide NCD-focused training at the involved health facilities to ensure high-quality care for participants referred to the responsible health facilities.

9.4 Reporting

CC-VHWs will document SAEs and AESIs in dedicated electronic case report forms (eCRFs) with subsequent assessment and classification by the study physician. All deaths and all other SAEs that are

possibly, probably or definitely related to the study intervention will be reported to at least one of the two principal investigators within one month after the study physician has become aware of the event. All deaths and all other SAEs that are possibly, probably or definitely related to the study intervention will be reported to the NHREC on a yearly basis.

10 STATISTICS

10.1 Hypothesis

aHT TwiC 1
Community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants is *safe and superior* with regard to BP control rates after twelve months compared to facility-based prescription in people living with *uncontrolled* aHT in rural Lesotho.

aHT TwiC 2
Community-based, CC-VHW-led, eHealth supported aHT care including the prescription of first-line antihypertensive SPCs for eligible participants is *safe and non-inferior* with regard to BP control rates after twelve months compared to facility-based prescription in people living with *controlled* aHT in rural Lesotho

10.2 Determination of sample size

The ComBaCaL cohort will consist of inhabitants of around 100 (range 90-112) randomly selected villages in rural Lesotho. The estimated mean number of adult ComBaCaL participants per village is 100 resulting in an estimated 10'000 adult cohort participants.
Sample size is calculated assuming an individual randomization inflated by a design effect that account for variation at cluster level, according to the code developed by Rotondi and Donner[20]. Based on preliminary results from an NCD prevalence survey in the region (NH-REC ID 139-2021), we expect the prevalence of aHT in the adult population in the rural setting in Lesotho to be around 18% with a control rate of 55%. Hence, considering an average cluster size of 100 adult inhabitants, the mean number of inhabitants with aHT is estimated to 18 (10 being controlled and 8 uncontrolled) with a standard deviation of 5. The sample size for both TwiCs was calculated separately with the higher of the two defining the overall intervention sample size.

10.2.1 aHT TwiC 1

In the intervention group, we assume a study consent rate of 75%, a probability of success of 60% among individuals that consent and 30% among those that do not consent. Hence, we estimate an overall success rate in the intervention group of 52.5%. We further assume an intra-cluster correlation of 0.015, a mean cluster size of 8 (standard deviation=5) and a probability of success of 35% in the control group. We calculate that a sample size of 304 (152 in each arm, 19 clusters per study arm) is required to detect superiority with a type I error of 0.025 and a statistical power of 80%.

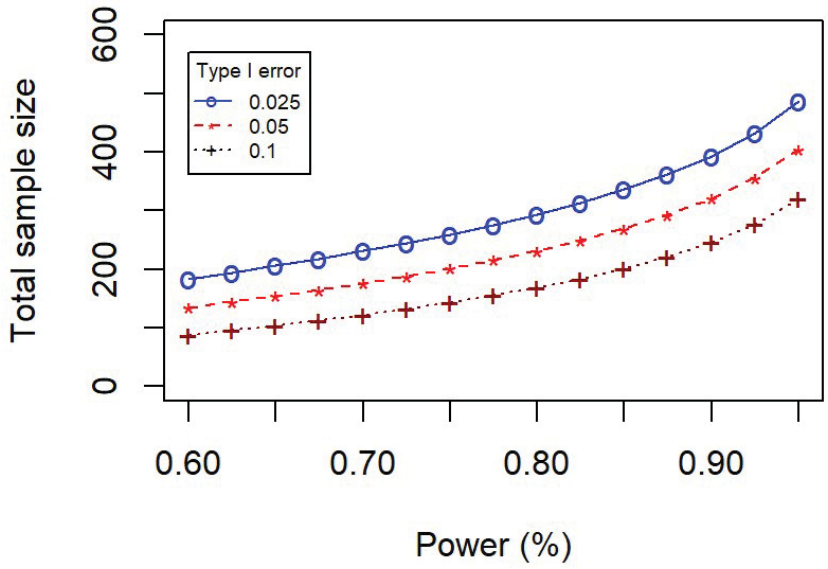

Figure 3 Individual sample size calculation for different power and type I error levels for aHT TwiC 1

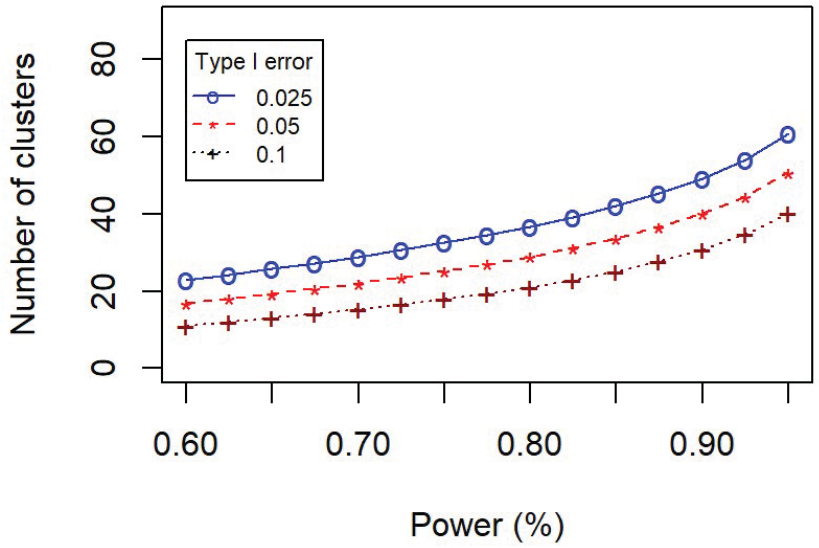

Figure 4 Cluster sample size calculation for different power and type I error levels for aHT TwiC 1

10.2.2 aHT TwiC 2

We set the non-inferiority margin for the odds ratio (OR) of reaching the primary endpoint to 0.58. On an absolute scale, this margin corresponds to a higher probability of failing to reach the primary outcome of 10 % in the intervention compared to the control group, assuming that the probability of success for the participants enrolled in the control arm is 80%. We assume an intra-cluster correlation of 0.015, a mean cluster size of 10 (standard deviation=5) and a probability of success of 80% in both intervention and control groups. This implies a sample size of 780 across 78 clusters (390 in each arm, 39 clusters per study arm) to be able to detect non-inferiority with a type I error of 0.025 and a statistical power of 80%. We inflate the calculated maximal number of cluster among the two TwiCs by 25% in order to account for uncertainties in the estimates of aHT prevalence, number of ComBaCaL village inhabitants and the consent rate. We finally aim to recruit 100 clusters (50 per study arm) for a total of 800 participants with uncontrolled aHT (TwiC 1) and 1000 participants with controlled aHT (TwiC2).

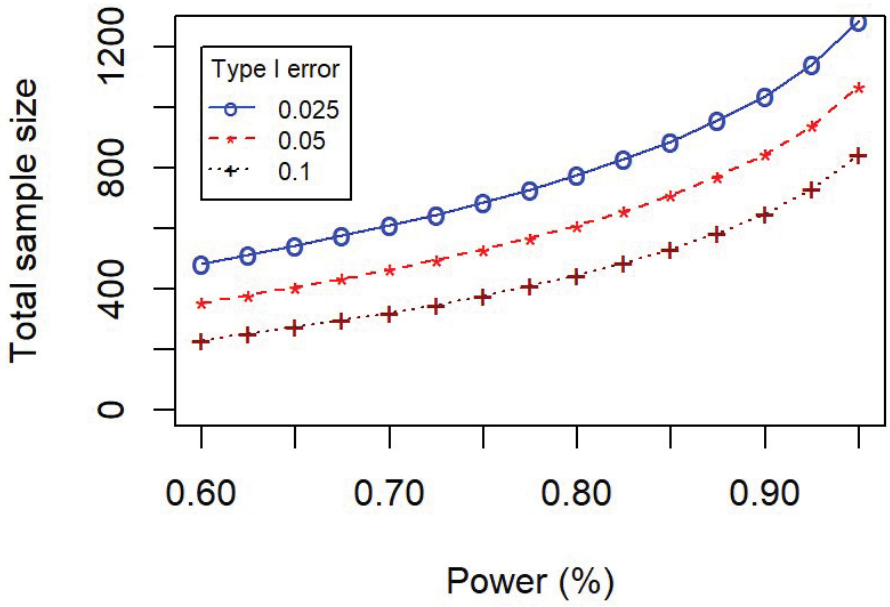

Figure 5 Individual sample size calculation for different power and type I error levels for aHT TwiC 2

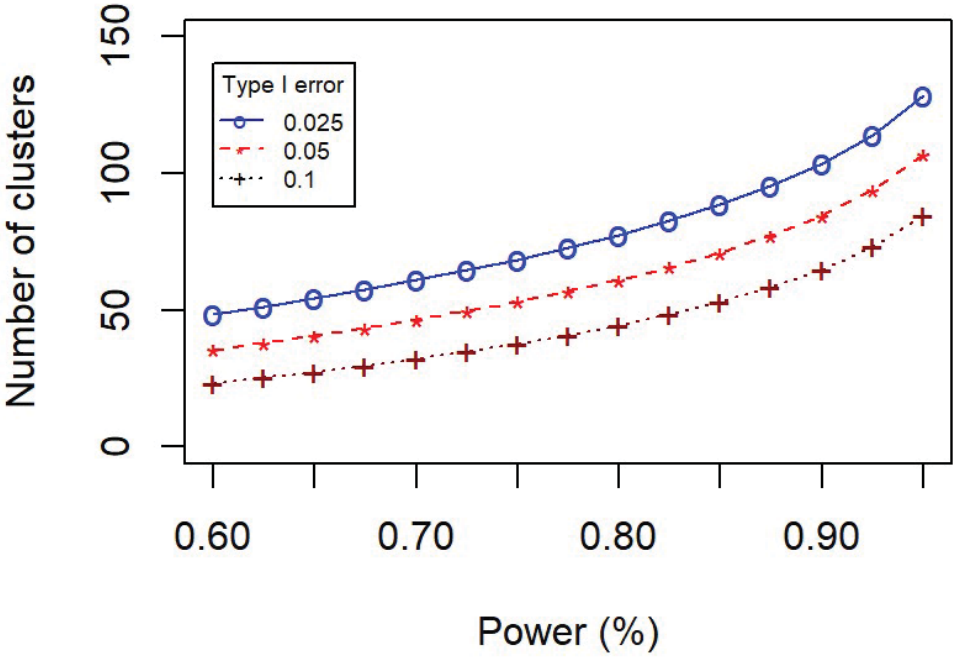

Figure 6 Cluster sample size calculation for different power and type I error levels for aHT TwiC 2

10.3 Description of statistical methods

Analyses will be performed following the principles for analysis of cluster-randomized trials in health research as outlined by Donner and Klar[43].
All analyses will be done using Stata[44] or R[45].

10.3.1 Datasets to be analysed, analysis populations

For both TwiCs, the *intention-to-treat (ITT)* set includes all participants as allocated per random selection of villages except those with reported pregnancy, a documented move out of the village, or traumatic death during the follow-up period who will be excluded. Participants with missing values (excluding

those moved out and those with traumatic death and those pregnant) will be considered as not having reached the endpoint of BP < 140/90 mmHg.
For both TwiCs the *per-protocol (PP)* set includes all participants who linked to care according to the group specific procedure (i.e. all participants in intervention villages with at least one clinical visit in relation to aHT management by a CC-VHW and in the control villages, participants with at least one clinical visit in relation to aHT management at a health centre). Participants with missing values (excluding those moved out or those becoming pregnant and those with traumatic death during follow-up) will be considered as not having reached the endpoint of BP < 140/90 mmHg.
For both TwiCs, the *complete case ITT* set includes the same population as the ITT set. However, participants with missing endpoint data will be excluded instead of being considered as not having reached the endpoint of BP <140/90 mmHg.
For both TwiCs, the *complete case PP* set includes the same population as the PP set. However, participants with missing endpoint data will be excluded instead of being considered as not having reached the endpoint of <140/90mmHg.
For TwiC 1, we are considering a Complier Average Causal Effect (CACE) analysis to assess the impact of compliance with the intervention as this provides a more unbiased treatment effect than a per protocol or as-treated analysis and the underlying assumptions for such an instrumental variable approach are given. We will obtain the CACE estimator using a "two-stage least squares" (TSLS) approach, which jointly models the two processes of participation and outcome (i.e. regression model of participation, and regression model predicting the outcome, given participation). Such a TSLS approach yields more accurate estimates and confidence intervals, than simply dividing the mean effect estimate by the proportion of compliers.[46]

10.3.2 Primary analysis

We will use a mixed effect logistic regression model with random intercept at the level of the clusters to assess the effect of the intervention.

10.3.2.1 aHT TwiC 1

Superiority will be assessed according to the 95% confidence interval of the odds ratio of the intervention of the ITT analysis.

10.3.2.2 aHT TwiC 2

Non-inferiority will be assessed according to the 95% confidence interval of the odds ratio of the intervention of the ITT and the PP analysis and the pre-defined non-inferiority margin. Further details will be provided in the statistical analysis plan (SAP).

10.3.3 Secondary analysis

Secondary endpoints will be reported using descriptive statistics such as mean and 95% Wald confidence intervals, frequency and percentages.
Further details will be outlined in the SAP.

10.4 Handling of missing data

Participants with missing outcomes due to traumatic death, pregnancy or after documented moving out of the village, will be excluded from the analyses.
Missing outcomes due to atraumatic death or without any documentation will be regarded as a negative outcome (i.e. as not meeting the target of 140/90mmHg) in both the ITT and the PP populations.
In the complete case analyses, only participants with observed outcomes will be considered. Further details of missing data will be outlined in the statistical analysis plan (SAP).

11 DESCRIPTION OF DATA MANAGEMENT

We refer to the current version of the “ComBaCaL cohort study protocol” for the description of data management. For this TwiC no other procedures than the ones outlined there apply.

12 QUALITY CONTROL AND QUALITY ASSURANCE

We refer to the current version of the “ComBaCaL cohort study protocol” for the description of quality control and quality assurance. For this TwiC no other procedures than the ones outlined there apply.

13 ETHICAL CONSIDERATIONS

13.1 Independent Ethics Committees (IECs)

This protocol and any protocol amendments will be reviewed and approved by the National Health Research Ethics Council (NH-REC) of Lesotho and by the Ethics Committee of Northern and Central Switzerland (EKNZ) before implementation.

13.2 Risk-benefit ratio

There is no substantial health risk associated with participation in this study. The aHT screening, diagnosis and management offered will conducted in line with national and international recommendations. All participants found to be at risk for a relevant medical condition will be referred to the responsible health facility for professional work-up and care.
Data collection will entail questionnaires, automated BP measurements, capillary blood measurements for lipid status. These procedures do not have the potential to cause significant harm to participants.
No personalized data of participants will be shared with people other than the directly involved study team members if not agreed upon by the participant.
The access to guideline-conform active community-based NCD screening will likely increase early case detection and thus improve access to potentially life-saving treatment. Additionally, follow-up in the community by CC-VHWs with re-linking services is likely to improve aHT care for participants.
Potential risks associated with the TwiC intervention include inadequate management by lay CC-VHWs. We will minimize this risk by assuring adequate training, continuous supervision by health care professionals, and close guidance through the ComBaCaL eHealth application. Community-based care delivery is widely implemented in HIV care in Lesotho providing substantial benefits compared to purely clinic-based care.
The evidence generated in this study may inform future national and international clinical guidelines to improve NCD care in low-resource settings. Additionally, the community-based activities provide the added benefit of building a healthy and friendly community environment through community advocacy and participation, and may help to raise awareness and knowledge of NCDs within participating villages. Thus, the ComBaCaL project is likely to have a direct positive impact on health outcomes of participants as well as generating evidence to improve context-specific NCD care on a longer perspective.
This project will be carried out in accordance with the research plan outlined in this protocol and with principles enunciated in the current version of the Declaration of Helsinki as well as all national legal requirements and guidelines as applicable.

13.3 Participant information and consent

The ComBaCaL cohort consent is based on the cmRCT[18] approach, i.e. all cohort participants consent to being randomized as part of a TwiC. Participant information and consent seeking for the ComBaCaL cohort will be conducted by the local ComBaCaL VHW in a three-stepped approach, first orally on village level, secondly orally on household level, and thirdly in written electronic form on individual level. We refer to the “ComBaCaL cohort study protocol” for details.
Participants that are being randomized to the control group, will not be bothered and data collected within the scope of the ComBaCaL cohort will be used for the TwiC analysis, too without further TwiC-specific information or consent. For villages randomized into the TwiC intervention group, an oral village consent from the village chief will be sought before the intervention will be offered to eligible individuals in the community. Participants may decline any of the offered services without implications on further cohort affiliation and their data will also be used for TwiC analyses. As the intervention does not entail any activities other than the task-shifting of standard-of-care aHT management components from primary healthcare professionals to CC-VHWs, oral intervention consent will be sought as outlined in the “ComBaCaL cohort study protocol”. Before the delivery of services (i.e. the prescription of medications), the CC-VHWs will provide the participants with information about the risks and benefits of the respective care component. The completeness of information provided will be documented with a checkbox in the

ComBaCaL app. In addition, the participants will be asked whether they are willing and ready to accept the care component offered. The participants may freely accept or refuse any care component offered or ask for more time for consideration until a follow-up visit a few days later. Only after documentation of the participants' readiness in the ComBaCaL app by the CC-VHWs the prescription of medications will be possible.

Participants will be able to reject care by the CC-VHW in the village at any time during the study and request referral to a health facility. Participants consenting to participation but subsequently rejecting care offered by the CC-VHW might be approached for qualitative inquiry on the reasons for the refusal of community-based care.

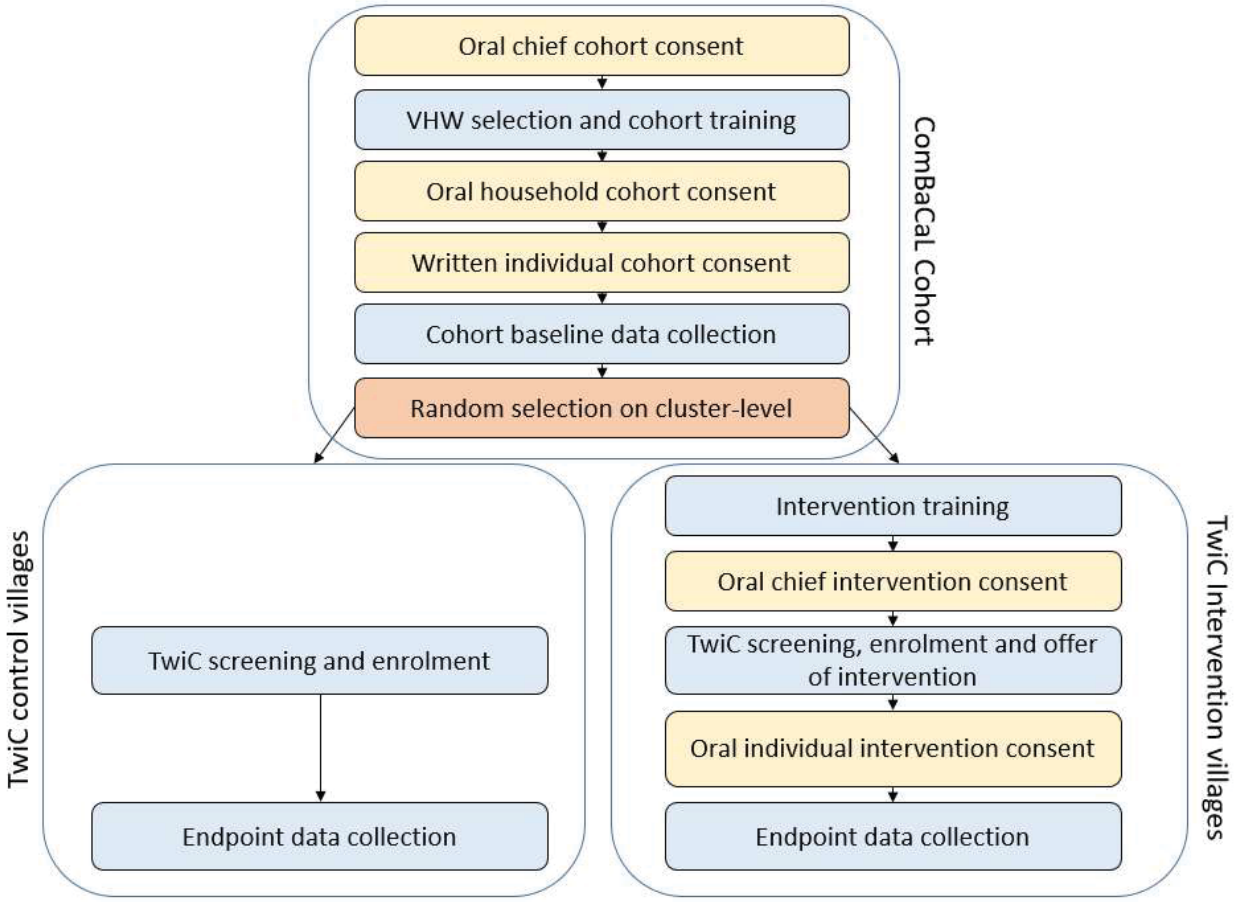

Figure 7 Consent cascade in ComBaCaL cohort and TwiC. Yellow: Consent, Orange: Randomization, Blue: Training or field activity

Withdrawal on household or individual level

ComBaCaL cohort consent can be withdrawn any time on individual or household (by household head) level without justification. No specific consent for the TwiC intervention will be sought at household level. Data collected until the time of withdrawal will be retained in the database.

Service delivery for people declining consent

CC-VHWs will offer the same screening, diagnostic and referral services to participants declining the intervention in intervention villages as in control villages.

13.4 Participant confidentiality

The investigators will ensure that the participants' confidentiality will be maintained at all times during and after the study, following procedures outlined in section 6.1 (enrolment procedures) and section 8 (data management).

13.5 Participants requiring particular protection

Pregnant women with aHT will not be included in the intervention but being referred to the responsible health facility for further assessment and management. The same applies to people with a severe comorbidity with an estimated life-expectancy of less than one year.
This study has a strong service delivery aspect and often people with mental or physical conditions impairing capacity for informed consent are particularly vulnerable to NCDs such as aHT and its complications. Therefore, we will offer the intervention also to eligible people with impaired judgement if an oral guardian consent for the intervention is provided.

13.6 Participant compensation

No compensation will be paid for participation in the study.

14 FUNDING

This research project is funded by the Swiss Agency for Development and Cooperation (SDC) and by the World Diabetes Foundation (WDF), through grants issued to SolidarMed. A written agreement between SolidarMed and the Division of Clinical Epidemiology of the University Hospital Basel defines the terms for the collaboration on the research aspects of the project. The funding sources are not involved in the study design, data collection, data analysis, interpretation of the results, or writing the manuscript. The study will be embedded in the SolidarMed Lesotho programme and will thus benefit from logistics and human resources of this organisation. The listed co-investigators have no conflicts of interest.

15 DISSEMINATION OF RESULTS AND PUBLICATION POLICY

15.1 Dissemination to scientific community

International scientific conferences and publications in scientific peer-reviewed journals will serve for wider dissemination of results. Preference will be given to journals with an open-access publication model. Further, anonymised datasets will be made available on open data repositories, such as www.zenondo.org. The study will be registered on ClinicalTrials.gov prior to the start of the trial and a summary of the study protocol will be published in a peer-reviewed journal. The current version of the International Committee of Medical Journal Editors (ICMJE) recommendations is applicable regarding authorship eligibility.[47] The use of professional writers is not intended.

15.2 Information of community and policy makers

Results of this study will be shared with stakeholders at district and national level. In Lesotho, health care workers and stakeholders will be informed about the findings during district meetings headed by the District Health Management Team (DHMT) and at national level, the national research symposium of the MoH and the NCD Technical Working Group will serve as platforms to share the results and discuss their implications among the policy makers.

16 APPENDIX

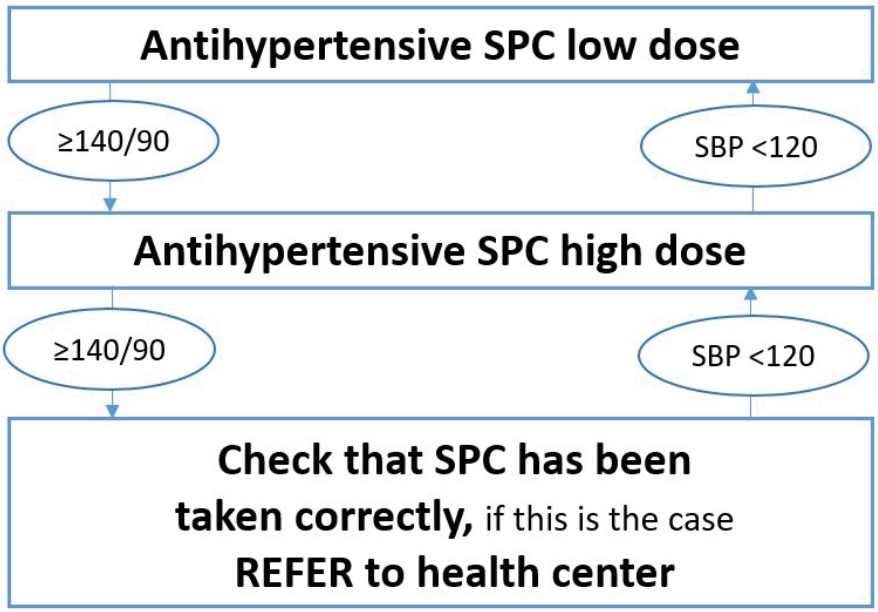

Figure 8 Treatment algorithm for uncomplicated hypertension. BP: Blood pressure, SPC: Single-pill combination, SBP: Systolic blood pressure, CVD: Cardiovascular disease

In ComBaCaL intervention villages, participants diagnosed with aHT without contraindications will be offered antihypertensive pharmacotherapy according to the algorithm above.
The molecules included in the antihypertensive SPC will be in line with the then valid Lesotho Standard Treatment Guidelines and with the selection of drugs that is available locally in routine primary healthcare. At the time of writing of this protocol, the Standard Treatment Guidelines of Lesotho were still at a draft stage and the Ministry of Health (MoH) of Lesotho was still in discussions about which SPC to procure, hence we are not specifying it here. According to the current draft version of the Lesotho Standard Treatment Guidelines, a combination of a calcium channel blocker (amlodipine) and a thiazide-like diuretic (hydrochlorothiazide or indapamide) will be used.
For the BP check-ups, the participant will be advised to rest and sit with the back supported. The average of the last two of three measurements will be considered (see current version of the ComBaCaL cohort protocol for details regarding BP measurements and the diagnostic algorithms applied).
Participants with high CVD risk, and no contraindications will be offered a lipid-lowering treatment using a statin in a fire-and-forget approach. High CVD risk among the participants diagnosed with aHT is defined as additionally having a history of stroke or myocardial infarction, having DM or chronic kidney disease (CKD) or being 50 years or older and having one or both of the following risk factors: BMI ≥ 30 kg/m^2, currently smoking. The molecule used will be in line with the Lesotho Standard Treatment Guidelines and with what is locally available in routine primary healthcare.
Participants with a history of myocardial infarction or stroke will be offered antiplatelet treatment using aspirin in line with the Lesotho Standard Treatment Guidelines.
At every visit, the CC-VHW will ask the participant about the current medication, adherence, potential side effects and contraindications against the treatment offered. This data will be documented in the ComBaCaL app.
Participants will be referred to a health facility for further care in case of complicated disease, unclear conditions, side effects against the antihypertensive treatment provided or if participants are not reaching treatment targets under the provided first-line treatment.

17 REFERENCES

1 Murray CJL, Aravkin AY, Zheng P, *et al.* Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet* 2020; **396**: 1223–49.

2 Roth GA, Mensah GA, Johnson CO, *et al.* Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020; **76**: 2982–3021.

3 Gouda HN, Charlson F, Sorsdahl K, *et al.* Burden of non-communicable diseases in sub-Saharan Africa, 1990–2017: results from the Global Burden of Disease Study 2017. *Lancet Glob Health* 2019; **7**: e1375–87.

4 Zhou B, Carrillo-Larco RM, Danaei G, *et al.* Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *The Lancet* 2021; **398**: 957–80.

5 Geldsetzer P, Manne-Goehler J, Marcus M-E, *et al.* The state of hypertension care in 44 low-income and middle-income countries: a cross-sectional study of nationally representative individual-level data from 1·1 million adults. *The Lancet* 2019; **394**: 652–62.

6 Kontis V, Cobb LK, Mathers CD, Frieden TR, Ezzati M, Danaei G. Three Public Health Interventions Could Save 94 Million Lives in 25 Years: Global Impact Assessment Analysis. *Circulation* 2019; **140**: 715–25.

7 Mbuthia GW, Magutah K, Pellowski J. Approaches and outcomes of community health worker's interventions for hypertension management and control in low-income and middle-income countries: systematic review. *BMJ Open* 2022; **12**: e053455.

8 Schwalm J-D, McCready T, Lopez-Jaramillo P, *et al.* A community-based comprehensive intervention to reduce cardiovascular risk in hypertension (HOPE 4): a cluster-randomised controlled trial. *The Lancet* 2019; **394**: 1231–42.

9 Augustovski F, Chaparro M, Palacios A, *et al.* Cost-Effectiveness of a Comprehensive Approach for Hypertension Control in Low-Income Settings in Argentina: Trial-Based Analysis of the Hypertension Control Program in Argentina. *Value Health* 2018; **21**: 1357–64.

10 Kostova D, Spencer G, Moran AE, *et al.* The cost-effectiveness of hypertension management in low-income and middle-income countries: a review. *BMJ Glob Health* 2020; **5**: e002213.

11 Jafar TH, Gandhi M, de Silva HA, *et al.* A Community-Based Intervention for Managing Hypertension in Rural South Asia. *N Engl J Med* 2020; **382**: 717–26.

12 Zack R, Okunade O, Olson E, *et al.* Improving Hypertension Outcome Measurement in Low- and Middle-Income Countries. *Hypertension* 2019; **73**: 990–7.

13 Gupta AK, Arshad S, Poulter NR. Compliance, Safety, and Effectiveness of Fixed-Dose Combinations of Antihypertensive Agents: A Meta-Analysis. *Hypertension* 2010; **55**: 399–407.

14 Fernández LG, Firima E, Robinson E, *et al.* Community-based care models for arterial hypertension management in non-pregnant adults in sub-Saharan Africa: a literature scoping review and framework for designing chronic services. *BMC Public Health* 2022; **22**: 1126.

15 He J, Irazola V, Mills KT, *et al.* Effect of a Community Health Worker–Led Multicomponent Intervention on Blood Pressure Control in Low-Income Patients in Argentina: A Randomized Clinical Trial. *JAMA* 2017; **318**: 1016.

16 WHO CVD Risk Charts Working Group. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health* 2019; **7**: e1332–45.

17 WHO. HEARTS Technical package for cardiovascular disease management in primary healthcare - Risk-based CVD management. Copenhagen: World Health Organization. Regional Office for Europe, 2021 https://apps.who.int/iris/handle/10665/338530 (accessed Sept 24, 2022).

18 Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ* 2010; **340**: c1066.

19 van der Velden JM, Verkooijen HM, Young-Afat DA, *et al.* The cohort multiple randomized controlled trial design: a valid and efficient alternative to pragmatic trials? *Int J Epidemiol* 2016; : dyw050.

20 Rotondi M, Donner A. Sample size estimation in cluster randomized trials: An evidence-based perspective. *Comput Stat Data Anal* 2012; **56**: 1174–87.

21 Bigna JJ, Noubiap JJ. The rising burden of non-communicable diseases in sub-Saharan Africa. *Lancet Glob Health* 2019; **7**: e1295–6.

22 Noncommunicable Diseases. WHO Reg. Off. Afr. https://www.afro.who.int/health-topics/noncommunicable-diseases (accessed Sept 13, 2021).

23 Lewin S, Munabi-Babigumira S, Glenton C, *et al.* Lay health workers in primary and community health care for maternal and child health and the management of infectious diseases. *Cochrane Database Syst Rev* 2010; published online March 17. DOI:10.1002/14651858.CD004015.pub3.

24 Mwai GW, Mburu G, Torpey K, Frost P, Ford N, Seeley J. Role and outcomes of community health workers in HIV care in sub-Saharan Africa: a systematic review. *J Int AIDS Soc* 2013; **16**: 18586.

25 Dave S, Peter T, Fogarty C, Karatzas N, Belinsky N, Pant Pai N. Which community-based HIV initiatives are effective in achieving UNAIDS 90-90-90 targets? A systematic review and meta-analysis of evidence (2007-2018). *PLOS ONE* 2019; **14**: e0219826.

26 Joseph JK, Rigodon J, Cancedda C, *et al.* Lay health workers and HIV care in rural Lesotho: a report from the field. *AIDS Patient Care STDS* 2012; **26**: 141–7.

27 Healthcare - Lesotho Review 2015 Edition. 2017; published online June 10. http://www.lesothoreview.com/healthcare-2015.php (accessed June 10, 2017).

28 Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2021. 2021. https://www.unaids.org/en/resources/documents/2021/2021_unaids_data (accessed Dec 14, 2021).

29 Kasaie P, Weir B, Schnure M, *et al.* Integrated screening and treatment services for HIV, hypertension and diabetes in Kenya: assessing the epidemiological impact and cost-effectiveness from a national and regional perspective. *J Int AIDS Soc* 2020; **23**. DOI:10.1002/jia2.25499.

30 Sando D, Kintu A, Okello S, *et al.* Cost-effectiveness analysis of integrating screening and treatment of selected non-communicable diseases into HIV/AIDS treatment in Uganda. *J Int AIDS Soc* 2020; **23 Suppl 1**: e25507–e25507.

31 D'Agostino RB, Vasan RS, Pencina MJ, *et al.* General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. *Circulation* 2008; **117**: 743–53.

32 Hajifathalian K, Ueda P, Lu Y, *et al.* A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol* 2015; **3**: 339–55.

33 Wagner RG, Crowther NJ, Micklesfield LK, *et al.* Estimating the burden of cardiovascular risk in community dwellers over 40 years old in South Africa, Kenya, Burkina Faso and Ghana. *BMJ Glob Health* 2021; **6**: e003499.

34 Feng Y-S, Kohlmann T, Janssen MF, Buchholz I. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res* 2021; **30**: 647–73.

35 Mostafavi F, Najimi A, Sharifirad G, Golshiri P. Beliefs About Medicines in Patients with Hypertension: the Instrument Validity and Reliability in Iran. *Mater Socio Medica* 2016; **28**: 298.

36 Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health* 1999; **14**: 1–24.

37 Craig CL, Marshall AL, Sj??Str??M M, *et al.* International Physical Activity Questionnaire: 12-Country Reliability and Validity: *Med Sci Sports Exerc* 2003; **35**: 1381–95.

38 Cultural adaptation - International Physical Activity Questionnaire. https://sites.google.com/site/theipaq/cultural-adaptation (accessed July 11, 2022).

39 Okeyo AP, Seekoe E, de Villiers A, Faber M, Nel JH, Steyn NP. Dietary Practices and Adolescent Obesity in Secondary School Learners at Disadvantaged Schools in South Africa: Urban–Rural and Gender Differences. *Int J Environ Res Public Health* 2020; **17**: 5864.

40 Ueda P, Woodward M, Lu Y, *et al.* Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. *Lancet Diabetes Endocrinol* 2017; **5**: 196–213.

41 Unger T, Borghi C, Charchar F, *et al.* 2020 International Society of Hypertension Global Hypertension Practice Guidelines. ; : 24.

42 Mancia G, Rosei EA, Azizi M, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. ; : 98.

43 Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold, 2000.

44 StatCorp L. Stata Statistical Software: Release 17. 2021. https://www.stata.com.

45 R Core Team. R: A language and environment for statistical computing. 2020. https://www.R-project.org/.

46 Stuart EA, Perry DF, Le H-N, Ialongo NS. Estimating Intervention Effects of Prevention Programs: Accounting for Noncompliance. *Prev Sci* 2008; **9**: 288–98.

47 International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. http://www.ICMJE.org (accessed Dec 19, 2021).