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

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Posted Date: April 9th, 2024

DOI: https://doi.org/10.21203/rs.3.rs-3805346/v1

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Abstract

Background

Arterial hypertension (aHT) is a major cause for premature morbidity and mortality. Control rates remain poor, especially in low- and middle-income countries. Task-shifting to lay village health workers (VHWs) and the use of digital clinical decision support systems may help to overcome the current aHT care cascade gaps. However, evidence on the effectiveness of comprehensive VHW-led aHT care models, in which VHWs provide antihypertensive drug treatment and manage cardiovascular risk factors is scarce.

Methods

Using the trials within cohort (TwiCs) design, we are assessing the effectiveness of VHW-led aHT and cardiovascular risk management in two 1:1 cluster-randomized trials nested within the Community Based Chronic Disease Care Lesotho (ComBaCaL) cohort study (NCT05596773). The ComBaCaL cohort study is maintained by trained VHWs and includes the consenting inhabitants of 103 randomly selected villages in rural Lesotho. After community-based aHT screening, adult, non-pregnant ComBaCaL cohort participants with uncontrolled aHT (blood pressure (BP) ≥140/90 mmHg) are enrolled in the aHT TwiC 1 and those with controlled aHT (BP <140/90 mmHg) in the aHT TwiC 2. In intervention villages, VHWs offer lifestyle counselling, basic guideline-directed antihypertensive, lipid-lowering, and antiplatelet treatment supported by a tablet-based decision support application to eligible participants. In control clusters, participants are referred to a health facility for therapeutic management. The primary endpoint for both TwiCs is the proportion of participants with controlled BP levels (<140/90 mmHg) 12 months after enrolment. We hypothesize that the intervention is superior with regard to BP control rates in participants with uncontrolled BP (aHT TwiC 1) and non-inferior in participants with controlled BP at baseline (aHT TwiC 2).

Discussion

The TwiCs were launched on September 08, 2023. On December 11, 2023, 371 and 673 participants were enrolled in TwiC 1 and TwiC 2. To our knowledge, these TwiCs are the first trials to assess task-shifting of aHT care to VHWs at community level, including the prescription of basic antihypertensive, lipid-lowering, and antiplatelet medication in Africa. The ComBaCaL cohort and nested TwiCs are operating within the routine VHW program and countries with similar community health worker programs may benefit from the findings.

Trial registration

The trial is registered on clinicaltrials.gov (NCT05684055; January 04, 2023).
Introduction

Globally, arterial hypertension (aHT) is the single most important risk factor for premature mortality, accounting for 10.8 million or almost 20% of all deaths in 2019 (1, 2). Low- and middle-income countries (LMICs) bear a disproportionate and growing share of the burden of aHT, while many high-income countries have managed to reduce the burden of aHT substantially over the past decades (1, 3–5). Besides changes in demography and lifestyle, insufficient preventive and therapeutic health system responses are main drivers for the disproportionally high cardiovascular morbidity and mortality in LMICs. This results in massive treatment gaps, with less than 20% of people living with aHT in LMICs reaching treatment targets (6–8). Through improved access to antihypertensive medication alone, about 40 million deaths could be prevented over the next 25 years (9). The involvement of VHWs may be an effective and sustainable approach to enhance access to aHT care and VHW-delivered aHT screening, monitoring, education and lifestyle counselling has been assessed in various settings with positive effects on awareness, treatment adherence, cardiovascular risk and blood pressure (BP) control rates (10–13). However, compared to community-based interventions by healthcare professionals, the effect of community-based VHW-led interventions on BP reduction was modest, probably because most of the VHW-led interventions did not include pharmacological treatment components (13).

Digital clinical decision support systems (CDSS) (14–17) and simple, evidence-based treatment protocols using antihypertensive single-pill combinations (SPCs) are promising facilitators for a sustainable task-shifting of more comprehensive services to lay VHWs (18, 19). However, it remains unclear how the use of CDSSs and antihypertensive SPCs can be included safely and effectively in community-based VHW-led aHT care, complementing the screening, counselling and referral services for which benefit has already been shown (20, 21).

We assess the effectiveness of a VHW-led, CDSS-assisted aHT care model in rural Lesotho in two cluster-randomized trials nested within the ComBaCaL (Community-Based Chronic disease care Lesotho) cohort study (NCT05596773). The ComBaCaL cohort is maintained by local, trained and supervised VHWs and is a platform for the investigation of chronic diseases and their management in rural Lesotho. The intervention described here has been developed based on a local non-communicable diseases prevalence survey and burden assessment (22, 23), a scoping literature review (24), multiple workshops with different stakeholders in Lesotho and the ComBaCaL pilot cohort study.

Methods

Setting

The ComBaCaL cohort study is conducted in 103 randomly selected villages in the two rural districts, Butha-Buthe and Mokhothlong, in Lesotho, a small, landlocked country surrounded by South Africa. In each ComBaCaL village, a VHW was elected by the inhabitants according to the procedures outlined in the Lesotho Ministry of Health Village Health Program policy (25). VHWs play an important role in the
Lesotho healthcare system by linking the community to facility-based health services. They are effectively contributing to the control of HIV/AIDS, especially in remote rural areas (25–27). Lesotho is a typical example of an African LMIC where a developing health system is facing the double burden of still highly prevalent infectious diseases (HIV/AIDS and tuberculosis) in combination with a rapidly growing non-communicable disease epidemic (23, 28–30).

Design and hypothesis

We are conducting two 1:1 cluster-randomized, open-label trials nested within the ComBaCaL cohort study following the trials within cohort (TwiCs) design (31, 32). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines were used to develop and report this protocol (33). The two TwiCs (aHT TwiC 1 and aHT TwiC 2) use the same cluster-randomization and the same intervention is applied. However, they test different primary hypotheses in distinct populations. The design and flow of events of the two TwiCs is presented in Fig. 1, using the Cluster Timeline Tool (34).

Primary hypothesis/estimand aHT TwiC 1

Offering community-based, VHW-led, CDSS-assisted aHT care in rural Lesotho is superior regarding BP control rates (proportion of participants reaching the treatment target < 140/90 mmHg) twelve months after enrollment compared to offering facility-based aHT care among non-pregnant adults with uncontrolled aHT (BP ≥ 140/90 mmHg) who did not experience a traumatic death and did not move out of their village irrespective of the uptake of the intervention, aHT treatment adherence, and adverse events.

Primary hypothesis/estimand aHT TwiC 2

Offering community-based, VHW-led, CDSS-assisted aHT care in rural Lesotho is non-inferior regarding BP control rates twelve months after enrollment compared to offering facility-based aHT care among non-pregnant adults with controlled aHT (BP < 140/90 mmHg) who did not experience a traumatic death and did not move out of their village irrespective of the uptake of the intervention, aHT treatment adherence and adverse events.

Eligibility and consent procedure

Participants for both TwiCs are recruited among the ComBaCaL cohort population, which includes all consenting inhabitants of the randomly selected ComBaCaL villages. Following the TwiCs design (31, 35), no additional written consent for the TwiCs is asked as the ComBaCaL cohort consent includes consent to being randomized for nested TwiCs assessing low-risk interventions. The participant information materials and the consent forms of the ComBaCaL cohort study (covering the nested TwiCs) are available from the corresponding author on request. As per cohort procedures (outlined in the ComBaCaL cohort study protocol, NCT05596773), all adult ComBaCaL cohort participants aged 18 years or older are screened for aHT by their VHW according to the diagnostic algorithm of the Lesotho Standard Treatment Guidelines (36).
All non-pregnant adult ComBaCaL cohort participants with aHT, defined as reporting intake of antihypertensive medication or being newly diagnosed during screening, are eligible for aHT TwiC 1 in case of uncontrolled BP levels (≥ 140/90) or for aHT TwiC 2 in case of controlled BP levels (< 140/90). Participants in the control group are followed according to the standard of care in the ComBaCaL cohort which includes aHT screening and referral to health facility based care in case of diagnosis. In the intervention group, diagnosed participants are offered the intervention by the VHW which they may accept or refuse in addition to the standard of care in the ComBaCaL cohort.

**Randomization and blinding**

Half of the ComBaCaL cohort villages are randomly allocated to the intervention group by a statistician not involved in the study. The random allocation is stratified by district (Butha-Buthe versus Mokhotlong) and access to health facilities (easy versus difficult access, defined as needing to cross a mountain or river or travel > 10 km to the nearest health facility). Due to the cluster-level randomization and TwiCs approach, participants are blinded to the allocation, meaning that participants in the control villages are not aware of the intervention being implemented in other villages. VHWs who are enrolling participants, providing the intervention, and collecting endpoint data are not blinded to the intervention. This partial blinding is reflected in Fig. 1. The statistician will be blinded for the primary endpoint analysis.

**Figure 1** Overview of the ComBaCaL cohort and aHT TwiCs 1 &2 using the Cluster Timeline Tool (34)

**Trial interventions**

In control villages, VHWs screen for aHT and confirmed cases are referred to the responsible health facility for further care. VHWs conduct a check-up with repeated referral (if required) six months after enrolment, as part of the routine ComBaCaL cohort care, with no further services provided at the community level.

In intervention villages, VHWs offer a community-based aHT care package that includes lifestyle counselling, prescription of antihypertensive SPCs containing amlopidipine and hydrochlorothiazide at low-dose (5mg/12.5mg) or high-dose (10mg/25g), lipid-lowering (atorvastatin 10mg) and antiplatelet (acetyl salicylic acid 100mg) treatment for eligible participants, and treatment support with regular check-ups for participants who are not reaching sufficient BP control with high-dose antihypertensive SPC or having a contraindication against the offered SPC. Guidance for treatment initiation and titration, drug prescription, counselling, and monitoring is provided via the ComBaCaL app, a specifically developed CDSS based on the current Lesotho Standard Treatment Guidelines (36) in line with international guidelines (37, 38). All activities conducted by VHWs, including counselling and drug prescription, are captured in the ComBaCaL app. VHWs may request support from supervising study staff or routine health care professionals at the responsible health facility. In case of insufficient BP control under high-dose antihypertensive SPC, unclear diagnosis, potential contraindications, side effects or the presence of clinical alarm signs or symptoms, the ComBaCaL app automatically suggests referral of participants to the health facility. Participants are free to accept or refuse the services offered by the VHW at any time.
Participants refusing VHW-led services are referred to the responsible health facility for further management with bi-monthly follow-ups by the VHW at the community level for treatment support.

All VHWs have received a two-week training on the ComBaCaL cohort procedures including usage of the ComBaCaL app, baseline data collection, reporting of relevant clinical events, and screening and diagnosis of aHT. VHWs in the intervention villages received an additional two-days training on the aHT intervention.

Endpoints

The selection of endpoints is based on the International Consortium for Health Outcomes Measurements’ data collection reference guide for hypertension in low- and middle-income countries V 4.0.0 (39). The primary endpoint is BP control rate, measured 12 months after enrolment. Secondary and exploratory endpoints are provided in Table 1. For all endpoints measured after six months, a window of 150 to 240 days, and for twelve months’ endpoints, a window of 300 to 420 days after enrolment applies.
### Table 1
Primary, secondary and exploratory endpoints.

**Primary endpoint:**

- Proportion of participants with controlled (<140/90 mmHg) blood pressure (BP) twelve months after enrolment

**Secondary endpoints:**

- 10-year risk for a fatal or non-fatal cardiovascular event estimated using the WHO cardiovascular disease risk prediction tool (40) six and twelve months after enrolment
- Proportion of participants with controlled BP (<140/90 mmHg) six months after enrolment
- Mean systolic (SBP) and diastolic (DBP) BP 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) (41), dietary habits using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa (42) and alcohol and tobacco use 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 antidiabetic medication as per prescription of a healthcare provider (VHW or healthcare professional) six and twelve months after enrolment or reaching treatment targets without intake of medication
- Occurrence of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) within six and twelve months after enrolment
- Self-reported adherence to antihypertensive treatment six and twelve months after enrolment

**Exploratory endpoints:**
### Primary endpoint:

- Quality of life using the EQ-5D-5L instrument (43) six and twelve months after enrolment
- Health beliefs using the Beliefs about Medicines Questionnaire adapted for people living with aHT (44,45) after twelve months
- Self-reported access to care and access to medication six and twelve months after enrolment
- Number of consultations at a health facility and with the VHW within six and twelve months after enrolment
- Trajectory of participants between facility-based and community-based care in the intervention villages (i.e. number of participants accepting community-based care at baseline, number of people switching to facility-based care and back to community-based care during the study period)
- 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 (BP < 140/90 mmHg) and are reporting no intake of antihypertensive medication after six and twelve months
- Proportion of eligible participants accessing lipid-lowering medication six and twelve months after enrolment
- Participants’, VHWs’ and involved health care professionals’ perception of the risks, benefits and problems of community-based management of uncomplicated aHT by VHWs
- Causes for the stop or interruption of treatment or switch to health facility-based treatment after initiation by 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 enrolment
- 10-year CVD risk estimated using the Globorisk score (46) and Framingham Risk Score (47) six and twelve months after enrolment
- Type and dosage of antidiabetic and lipid-lowering medications prescribed by VHWs or healthcare professionals six and twelve months after enrolment
- Proportion of participants with grade III hypertension (180/110 mmHg) six and twelve months after enrolment

**Abbreviations:** AESI: Adverse event of special interest; aHT: arterial hypertension; BMI: body mass index; BP: blood pressure; CVD: Cardiovascular disease; DBP: diastolic blood pressure; SAE: Serious adverse event; SBP: systolic blood pressure; VHW: Village health worker; WHO: World Health Organization.

Adverse events of special interest (AESIs) are defined as adverse events (AEs) consistent with aHT complications, such as stroke, myocardial infarction, hypertensive emergency, new diagnosis of heart failure or chronic kidney disease, and AEs probably related to intake of antihypertensive medication leading to discontinuation of the medication concerned.
Baseline and endpoint assessments are conducted by VHWs guided by the ComBaCaL app through instructions for correct BP measurement procedures, sample collection and structured questionnaires. BP measurements are conducted according to the Lesotho Standard Treatment Guidelines (36) using automated BP machines (Omron M3 Comfort [HEM7131-E] (48)). BP measurements are taken after determination of the correct cuff size in a sitting position after five minutes of rest with feet on the floor, the arm supported without talking or moving during the measurement. At the first visit, the reference arm is determined by measuring BP on both arms. The arm with higher systolic BP is identified as reference arm and used for all subsequent BP measurements. The BP value is calculated as the mean of the last two out of three consecutive measurements at intervals of one minute. For the diagnosis of aHT, two elevated measurements in the range of 140-179/90-109 mmHg on two different days are required or two measurements of 180/110 mmHg or higher on the same day, at least 30 minutes apart.

Some baseline data are extracted from the ComBaCaL cohort database, including sociodemographic characteristics, anthropometrics, targeted medical history, cardiovascular disease risk factors, physical activity using the validated International Physical Activity Questionnaire Short Form (IPAQ-SF) (41), dietary habits using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa (42) and self-reported alcohol and tobacco use (see Figure 1 and Table 2). After identification of eligible participants for the aHT TwiCs through BP screenings, further trial baseline data are collected including blood lipids, quality of life using the EQ-5D-5L instrument (43), health beliefs using the Beliefs about Medicines Questionnaire adapted for people living with aHT (44,45) and self-reported access to care.

**Table 2: Schedule of enrolment, interventions and assessments according to Standard Protocol Items: Recommendations for Intervventional Trials (SPIRIT) (33)**

Abbreviations: aHT: Arterial hypertension; BP: blood pressure CVDRF: Cardiovascular disease risk factor; T2D: Type 2 diabetes; TwiC: Trial within Cohort; LDL: Low-density lipoprotein; HDL: high-density lipoprotein; SPC: single-pill combination

Endpoint assessments through home visits by VHWs are scheduled six months (range 150 to 240 days) and twelve months (300 to 420 days) after TwiC enrolment. During follow-up visits, VHWs in both groups inquire about the occurrence of possible SAEs or AESIs and document them in the ComBaCaL app. In addition, VHWs may solicit AESIs and SAEs through reporting by participants, friends or relatives, screening of participants’ “bukanas” (personal health booklet) and reporting by routine health facility staff any time during the follow-up period.

Possible AESIs and SAEs flagged by the VHWs will be followed-up by supervising study staff to collect further clinical information (see Table 2). The pseudonymized reports will be submitted to the study physician who will remain blinded to the allocation. The study physician will classify the reports as SAEs, AESIs or neither of the two and conduct a causality assessment for events classified as SAEs or AESIs. In
<table>
<thead>
<tr>
<th>TIMEPOINT</th>
<th>-300 - 0 (Cohort Baseline)</th>
<th>0 (TwC Baseline)</th>
<th>150-240 (6-month follow-up)</th>
<th>300-420 (12-month follow-up)</th>
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<tr>
<td><strong>ComBaCaL cohort activities:</strong></td>
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<td>ComBaCaL cohort informed consent(^1)</td>
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<td>Date of birth</td>
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<tr>
<td>Height, weight, abdominal circumference</td>
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<tr>
<td>Targeted medical history</td>
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<td>CVDRFs(^2)</td>
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<tr>
<td>aHT Screening</td>
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<td>BP measurements</td>
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<td>Health beliefs(^3)</td>
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<td>Quality of life(^4)</td>
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<tr>
<td>Blood lipid status(^5)</td>
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<td>Screening for relevant clinical events</td>
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<td>Screening for clinical alarm signs/symptoms</td>
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<td>Referral to health facility if required</td>
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<td><strong>TwiC intervention:</strong></td>
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<tr>
<td>Provide lifestyle counselling</td>
<td>X</td>
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<tr>
<td>Provide treatment support&lt;sup&gt;7&lt;/sup&gt;</td>
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<tr>
<td>Referral to health facility if required&lt;sup&gt;8&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
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</table>

1: Including consent to participation in TwiCs
2: Physical activity using IPAQ-SF (41), dietary habits (42), tobacco and alcohol use
3: Using the Beliefs about Medicines Questionnaire (44,45)
4: Using the EQ-5D-5L instrument (43)
5: Total cholesterol, LDL, HDL, triglycerides
6: To participants eligible according to Lesotho Standard Treatment Guidelines (36)
7: To participants receiving treatment from health facility (i.e. participants using three or more antihypertensive drugs)
8: In case of insufficient BP control or clinical alarm symptoms

addition, questionnaires about participants’ satisfaction with and acceptability of the TwiCs intervention will be administered and semi-structured interviews conducted with a subsample of participants, VHWs and involved health care professionals to qualitatively explore perceived risks, benefits, problems and acceptability of community-based, VHW-led aHT care.

**Sample size**

Separate sample size calculations for the two TwiCs were performed with the higher of the two defining the overall sample size. Sample sizes were calculated assuming an individual randomization inflated by a design effect that accounts for variation at cluster level, according to Rotondi and Donner (49). Based on preliminary results from an non-communicable disease prevalence survey in Lesotho (22), we expect an adult prevalence of aHT in rural Lesotho of 18%. 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).

For aHT TwiC 1, testing the hypothesis that the intervention will lead to superior BP control rates among people with uncontrolled BP, we assume an acceptance rate of 75% in the intervention group (based on a previous study (50) and findings from the pilot cohort), a probability of BP control of 60% among individuals that accept the intervention and 30% among those refusing the intervention. Hence, we
assume an overall BP control rate in the intervention group of 52.5%. We further assume an intra-cluster correlation of 0.015 (50,51), a mean cluster size of 8 (standard deviation=5) and a probability of BP control of 35% in the control group (22). 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%.

For aHT TwiC 2, testing the hypothesis that the intervention will lead to non-inferior BP control rates among people with controlled BP at baseline, we assume an intra-cluster correlation of 0.015 (50,51), a mean cluster size of 10 (standard deviation=5) and a probability of BP control at 12 months of 80% in both intervention and control group. Based on considerations of clinical relevance, the non-inferiority margin is set to a 10% higher probability of failing to reach the primary outcome of BP control (<140/90 mmHg) in the intervention compared to the control group. This corresponds to an odds ratio (OR) of reaching the primary endpoint of 0.58 between the intervention and the 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 clusters among the two TwiCs by 25% to account for uncertainties in the estimates of aHT prevalence, number of ComBaCaL village inhabitants and the acceptance rate reaching a total number of 98 clusters. Due to operational reasons, we finally decided to recruit in all 103 ComBaCaL cohort villages, for a total of 824 participants with uncontrolled aHT (TwiC 1) and 1030 participants with controlled aHT (TwiC 2). Through repeated home visits by the VHWs, maximum recruitment within these 103 villages will be ensured while adding further villages in case the sample size is not reached is not possible.

Statistical analysis

Analyses will be performed following the principles for analysis of cluster-randomized trials in health research as outlined by Donner and Klar (52). For both TwiCs, we will use a mixed effect logistic regression model with random intercept at the level of the clusters.

The primary hypothesis of aHT TwiC 1 (superiority of the intervention in people with uncontrolled BP at baseline) will be assessed in a modified intention-to-treat analysis set, including all participants as randomized except those with pregnancy reported during follow-up, a documented move out of the village, or traumatic death during the follow-up.

The primary hypothesis of aHT TwiC 2 (non-inferiority of the intervention in people with controlled aHT at baseline) will be assessed according to the 95% confidence interval in the modified intention-to-treat analysis set as defined above and an appropriate per protocol analysis, such as a Complier Average Causal Effect (CACE) analysis (53) using causal inference techniques that will be defined in detail in the statistical analysis plan.

Secondary endpoints for both TwiCs will be reported using descriptive statistics such as the mean and 95% Wald confidence intervals, frequency and percentages. Further details will be outlined in the
Data management and monitoring

All ComBaCaL VHWs received a password-protected tablet with the ComBaCaL app installed. The ComBaCaL app serves as CDSS and data collection tool. It is based on the open source Community Health Toolkit Core Framework, a widely-used, offline-first, open source software toolkit designed for community health systems (54). Data are synchronized regularly to a secure server hosted at the University Hospital Basel, Switzerland. All shared data exports will be pseudonymized. Data are monitored locally by the VHW supervisors and centrally by the data management team of the University Hospital Basel. The intervention assessed in these TwiCs entails the task-shifting of aHT services according to local and international guidelines. It has a low risk profile and therefore neither the establishment of an external data monitoring committee nor a formal interim analysis is planned.

Discussion

Many countries in Africa and other LMICs have established VHW systems that are traditionally focusing on maternal and neonatal health and on communicable diseases, especially HIV/AIDS (55). In recent years, evidence has emerged showing a beneficial effect and high cost-effectiveness of VHW-based models for diseases outside the traditional scope, especially for non-communicable diseases (10,13,56,57). While VHW-based aHT care models focusing on educational, screening, monitoring and referral services have shown positive effects on linkage to care, adherence and BP levels, the effectiveness on BP reduction remained limited, probably due to the inability of VHWs to deliver pharmacological treatment (10,13,58). Recently, two landmark studies in China, Malaysia and Colombia have shown significant and clinically relevant reductions in BP levels and cardiovascular risk through community-based non-physician healthcare worker led multifaceted interventions including delivery of pharmacological treatment (59,60). However, the generalizability of these findings to the African context are limited. The study in China involved village health doctors with multi-year medical training and considerable clinical experience (60), a cadre that is not existing in most LMICs, especially in Africa. The study in Colombia and Malaysia relied on drug prescription by healthcare professionals and community health workers merely delivered the drugs, an approach that might limit effective scale-up. (61).

According to a recent scoping review, our two TwiCs will be the first to assess a multifaceted, community-based, VHW-led aHT care intervention including pharmacological treatment in Africa (24).

A strength of both TwiCs is their implementation within an established village cohort that is integrated into the local healthcare system. The study team will provide monitoring to ensure participant safety and data quality, but the intervention will be provided by VHWs recruited within the Lesotho Ministry of Health VHW program (25) and all parts of the intervention will be delivered according to the current Lesotho Standard Treatment Guidelines (36). The TwiCs design allows to assess the intervention under conditions close to real life: participants in control villages are not aware of the intervention in other villages, while
participants in intervention villages are being offered the intervention with oral consent, as it would be the case in routine care.

As per international recommendations (38), a holistic approach to cardiovascular disease management is applied; the intervention does not only include BP control measures, but consists of a comprehensive package including lifestyle counselling, lipid-lowering and antiplatelet treatment for those eligible, and the estimated 10-year risk for a cardiovascular event is a secondary outcome of both TwiCs. The two aHT TwiCs are implemented in parallel with another TwiC nested in the ComBaCaL cohort that is assessing a similar healthcare service package delivered by the same VHWs but for type 2 diabetes mellitus (62). This combination allows us to gather valuable experience and empirical evidence about implementing community-based integrated service delivery for two major non-communicable diseases simultaneously.

The World Health Organization guidelines on digital interventions for health system strengthening are recommending the use of mobile CDSS for health workers at the community level (63). However, a recent systematic review found that conclusive evidence on the effectiveness of digital health interventions on BP control in Africa is absent and that large randomized controlled trials are required to produce such (64). These two TwiCs will address this evidence gap.

The two TwiCs have several limitations. First, VHWs in control villages are also conducting BP screenings and offer regular referral services, as part of the routine cohort procedures, which in itself is an intervention and has to be considered when interpreting the results. Second, due to the multifaceted nature of the intervention, conclusions on the effects of individual components will be limited. Third, the randomization for the TwiCs happens before the identification of eligible trial participants, because VHWs in each arm need specific training before they identify the first participant in their village. This design choice brings two challenges: the possibility of empty clusters and the possibility of differential recruitment (65). Those challenges are minimized by VHWs systematically screening and diagnosing all ComBaCaL cohort participants in their villages during repeated home visits according to predefined algorithms and thus identifying all eligible TwiCs participants in their village irrespective of trial arm.

In summary, these TwiCs are assessing the effectiveness of a comprehensive, CDSS-supported, VHW-led, setting-adapted, community-based aHT intervention within the existing Lesotho Village Health Program. They will generate the evidence required for the future development of community-based aHT care models in Lesotho and similar settings.

**Trial status**

This manuscript is based on the approved study protocol version 1.1, dated February 07, 2023. Recruitment for the TwiCs started on September 08, 2023, and is ongoing. 371 participants with uncontrolled BP (≥140/90 mmHg) were enrolled in aHT TwiC 1 and 673 participants with controlled BP (<140/90 mmHg) were enrolled in aHT TwiC 2 on December 11, 2023, prior to submission of this manuscript. We expect enrolment to be completed by the end of April 2024.
Abbreviations

- AESI: Adverse event of special interest
- aHT: Arterial hypertension
- BMI: Body-mass index
- BP: Blood pressure
- CDSS: Clinical decision support system
- ComBaCaL: Community-Based chronic disease Care Lesotho
- CVDRF: Cardiovascular disease risk factor
- HDL: High density lipoprotein
- LDL: Low density lipoprotein
- LMICs: Low- and middle-income countries
- SAE: Serious adverse event
- SPC: Single-pill combination
- TwiC: Trial within Cohort
- VHW: Village Health Worker

Declarations

Ethics approval and consent to participate

These TwiCs were approved by the National Health Research and Ethics Committee (NH-REC) of Lesotho (ID 102-2022) and the Ethikkomission Nordwest- und Zentralschweiz (EKNZ) in Switzerland (ID AO_2022_00074). Protocol amendments will be communicated to the involved ethics committees and updated on clinicaltrials.gov.

Participants for the TwiCs are recruited among the ComBaCaL cohort population. All participants gave written informed consent with electronic signatures to participate in the ComBaCaL cohort study and to be randomly selected for nested TwiCs (31,35).

Consent for publication

Not applicable

Availability of data and materials

We will make pseudo-anonymized individual data freely available on a suitable repository, such as zenodo.org, along with publication of the study results. The full protocol as submitted to ethics
committees is available on clinicaltrials.gov. Study results will be published in a peer-reviewed journal without the use of professional writers and communicated to local health authorities and community stakeholders. Access to the test environment of the ComBaCaL app is available from the corresponding author upon reasonable request.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

These TwiCs are part of the ComBaCaL project which is funded by the TRANSFORM grant of the Swiss Agency for Development and Cooperation (project number 7F-10345.01.01) and a grant by the World Diabetes Foundation (WDF-1778). FG’s salary is funded through a personal MD/PhD grant by the Swiss National Science Foundation (grant number 323530_207035). AA’s salary is funded through a career grant of the University of Basel (Junior Research Fund). The funders had no role in the design of the TwiCs and will not have any role during its analyses, interpretation of the data, or decision to submit results.

**Authors' contributions**

AA and NDL are the principal investigators, they acquired the main funding, lead the project and substantially contributed to the manuscript. FG drafted the manuscript, leads the clinical development of the ComBaCaL app, supports the implementation, and conceptualized the TwiCs together with the principal investigators. RG (lead), TIL, MC, TK, MalebM, MalehM, MosM, MotM, ManM, MK, PMS, MB and RM are responsible for the local implementation of the TwiCs through training and supervision of VHWs and local data monitoring. TT, MK, MIH and FR supported the development of the ComBaCaL app and the training of VHWs. TL and GSS are responsible for central data management, SM for the local data management. MadM and SP are responsible for the collaboration with the Lesotho Ministry of Health and gave input on the study design of the TwiCs to ensure alignment with local guidelines and practices. DB and KK lead the technical development of the ComBaCaL app. TB reviewed and approved the clinical algorithms. MB gave substantial input on the study design. FC is the trial statistician and conducted the sample size calculations and is responsible for statistical analysis. All authors read and approved the final manuscript.

**Acknowledgements**

We would like to acknowledge the SolidarMed team in Lesotho and Switzerland, and the involved VHWs for their essential contributions to these TwiCs and the ComBaCaL project. Furthermore, we would like to
acknowledge the students from the Department of Informatics of the University of Zurich under the supervision of Dario Staehelin and Gerhard Schwabe who have contributed to the development of the pilot version of the ComBaCaL app.

References


Figures

Figure 1
Overview of the ComBaCaL cohort and aHT TwiCs 1 &2 using the Cluster Timeline Tool (34)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SpiritChecklistComBaCaLaHTTwiCs20240126.doc.docx