**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: two cluster-randomized trials within the ComBaCaL cohort study (ComBaCaL arterial hypertension TwiC 1 & ComBaCaL arterial hypertension TwiC 2)**

Trial registration: ClinicalTrials.gov, NCT05596773

# Statistical Analysis Plan

Date Prepared: 28/05/2024

Version: v.1.0

Author: Frédérique Chammartin

# CONTENTS

# 1 INTRODUCTION

This document provides a detailed description of the methodologies that will be followed, as closely as possible, when analysing and reporting results from the ComBaCaL arterial hypertension TwiC 1 & ComBaCaL arterial hypertension TwiC 2. The planned analysis detailed in this document complies with the "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 arterial hypertension TwiC 1 & ComBaCaL arterial hypertension TwiC 2) ", v.1.1, dated February 7, 2023.

The purpose of the plan is to:

a. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice in general, and minimises bias by preventing inappropriate post hoc analyses.
b. Ensure that the analyses performed are consistent with the study protocol.
c. Explain in detail how the data will be handled, covariates derived and analysed to enable others to perform the actual analysis in the event of sickness or other absence.
d. Protect the project by helping it keep to timelines and within scope.

# 2 DOCUMENT HISTORY

Amendments to the statistical analysis plan may become necessary as the trial progresses. This section contains the revision history of this document.

*Table 1) Document history summary.*

| Statistical Analysis Plan Version | Protocol Version | Section number(s) changed | Description of changes | Date Implemented |
|---|---|---|---|---|
| | | | | |
| 1.1 | 1.1 | NA | NA | 28.05.2024 |
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# 3 TRIAL SYNOPSIS

This section provides a short summary of the key aspect of the study. More details are provided in the following sections and, where appropriate, the protocol might be referenced for a full description.

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| **Title:** | ComBaCaL arterial hypertension TwiC 1 & ComBaCaL arterial hypertension TwiC 2 |
| **Design:** | 1:1 cluster-randomized, open-label trials nested within the ComBaCaL cohort study according to the Trials within Cohort (TwiCs) design |
| **Number of Patients:** | ComBaCaL arterial hypertension TwiC 1: minimally required sample size: 304 participants across 38 clusters.<br>ComBaCaL arterial hypertension TwiC 2: minimally required sample size: 780 participants across 78 clusters. |

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| | To account for uncertainties around arterial hypertension prevalence, number of inhabitants per village, consent rates, as well as for operational reasons, we decided to enroll participants from all 103 ComBaCaL cohort villages resulting in an anticipated maximum sample size of 824 and 1030 participants for TwiC 1 and TwiC 2, respectively. |
| **Number of Sites:** | 103 ComBaCaL cohort villages |
| **Study Duration:** | Enrolment started on September 9, 2023. Recruitment is planned to end in June 2024. Follow-up duration is 12 months (window 300-420 days) and will be completed by August 2025. |
| **Study population:** | ComBaCaL arterial hypertension TwiC 1: non-pregnant adult ComBaCaL cohort participants with arterial hypertension, defined as reporting intake of antihypertensive medication or being newly diagnosed during screening and with **uncontrolled** blood pressure levels at enrolment (systolic ≥140 mmHg or diastolic ≥90 mmHg).<br>ComBaCaL arterial hypertension TwiC 2: non-pregnant adult ComBaCaL cohort participants with arterial hypertension, defined as reporting intake of antihypertensive medication or being newly diagnosed during screening and with **controlled** blood pressure levels at enrolment (<140/90). |
| **Interventions:** | ComBaCaL arterial hypertension TwiC 1 & ComBaCaL arterial hypertension TwiC 2:<br>Participants living in villages randomized to the **control arm** will be referred by the village health workers to the responsible health facility and will benefit from a 6-month check up in the community by the village health worker with another referral if needed.<br>Participants living in villages randomized to the **intervention arm** will benefit from a community-based arterial hypertension care package delivered by the village health worker including lifestyle counselling, regular prescription and dispensing of antihypertensive single-pill combinations (SPCs), statin and aspirin if clinically indicated, and treatment support. Regular check-ups will be provided to participants not eligible for drug prescription by village health workers. |
| **Endpoints:** | <u>Primary</u><br>• Controlled blood pressure (<140 and <90 mmHg) at 12 months follow-up (ComBaCaL arterial hypertension TwiC 1 & ComBaCaL arterial hypertension TwiC 2)<br><u>Secondary</u><br>• 10-year risk for a fatal or non-fatal cardiovascular event estimated using the WHO cardiovascular disease risk prediction tool six and twelve months after enrolment<br>• Controlled blood pressure six months after enrolment<br>• Mean systolic (SBP) and diastolic (DBP) blood pressure six and twelve months after enrolment<br>• CVD risk factors, such as BMI, abdominal circumference, blood lipid status, physical activity using the validated International Physical Activity Questionnaire Short Form |

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| | (IPAQ-SF), dietary habits using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa, and alcohol and tobacco use six and twelve months after enrolment<br>• Linkage to care: proportion of participants not taking treatment at enrolment who have initiated pharmacological antihypertensive treatment six and twelve months after enrolment<br>• 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 (village health worker or healthcare professional) six and twelve months after enrolment or reaching treatment targets without intake of medication<br>• Occurrence of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) within six and twelve months after enrolment<br>• Self-reported adherence to antihypertensive treatment six and twelve months after enrolment<br><u>Exploratory</u><br>• Quality of life using the EQ-5D-5L instrument six and twelve months after enrolment<br>• Health beliefs using the Beliefs about Medicines Questionnaire adapted for people living with arterial hypertension after twelve months<br>• Self-reported access to care and access to medication six and twelve months after enrolment<br>• Number of consultations at a health facility and with the village health worker within six and twelve months after enrolment<br>• 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)<br>• Proportion of participants with arterial hypertension 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<br>• Proportion of participants who are reaching treatment targets (blood pressure <140/90 mmHg) and are reporting no intake of antihypertensive medication at six and twelve months follow-up<br>• Proportion of eligible participants accessing lipid-lowering medication six and twelve months after enrolment<br>• Participants', village health workers' and involved health care professionals' perception of the risks, benefits and problems of community-based management of |

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| | uncomplicated arterial hypertension by village health workers<br>• Causes for the stop or interruption of treatment or switch to health facility-based treatment after initiation by Village health workers in the community<br>• Health system costs and individual costs for participants for the management of their condition within the first six and twelve months after enrolment<br>• 10-year CVD risk estimated using the Globorisk score and Framingham Risk Score six and twelve months after enrolment<br>• Type and dosage of antihypertensive and lipid-lowering medications prescribed by Village health workers or healthcare professionals six and twelve months after enrolment<br>• Proportion of participants with grade III hypertension (180/110 mmHg) six and twelve months after enrolment |

# 4 TRIAL OVERVIEW

## 4.1 BACKGROUND AND RATIONALE

Arterial hypertension is a significant cause of premature illness and death in low-income countries where control rates are low. Task-shifting to village health workers and use of digital clinical decision support has the potential to improve the current arterial hypertension care cascade. Randomized evidence regarding the effectiveness of comprehensive village health worker-led arterial hypertension care models, where village health workers administer antihypertensive medications and address cardiovascular risk factors is needed to guide future development of community-based arterial hypertension care models in Lesotho and similar settings. We refer to the protocol for more details.

## 4.2 TRIAL DESIGN AND INTERVENTION

These are a 1:1 cluster-randomized, open-label trials within the ComBaCaL cohort study according to the TwiCs design. In the TwiCs design the initial cohort consent includes consent to randomization for nested trials. Participants allocated to the control arm of nested TwiCs are not informed of their participation in the trial and follow routine cohort procedures. The intervention (community-based management of hypertension and cardiovascular risk factors provided by the village health worker) is offered to participants allocated to the intervention arm; participants are free to accept the intervention. We refer to the protocol for further details.

## 4.3 OBJECTIVES

The two primary objectives are to 1) test superiority of the proposed village health worker model of care to the routine ComBaCaL cohort care in terms of blood pressure control rate at 12 months follow-up in adults with uncontrolled blood pressure levels (ComBaCaL arterial hypertension TwiC 1), and 2) test non-inferiority of the proposed village health worker model of care to the routine ComBaCaL cohort care in terms of blood pressure

control rates at 12 months follow-up in adults with controlled blood pressure levels (ComBaCaL arterial hypertension TwiC 2).

## 4.4 ELIGIBILITY CRITERIA

Inclusion Criteria

1. Individuals ≥18 years old that consent to the ComBaCaL cohort study (see ComBaCaL cohort study protocol, EKNZ ID 2022-00058, clinicaltrials.gov ID NCT05596773 for details on cohort description, and inclusion criteria).
2. ComBaCaL arterial hypertension TwiC 1: individuals with arterial hypertension defined as reporting intake of antihypertensive medication or being newly diagnosed with uncontrolled blood pressure levels at baseline (SBP ≥140 and/or DBP ≥90)
3. ComBaCaL arterial hypertension TwiC 2: individuals with arterial hypertension defined as reporting intake of antihypertensive medication or being newly diagnosed during screening and with controlled blood pressure levels at baseline (SBP<140 and DBP <90)

Inclusion to ComBaCaL arterial hypertension TwiC 1 and ComBaCaL arterial hypertension TwiC 2 are mutually exclusive.

Exclusion Criteria

1. Self-reported pregnancy at baseline

## 4.5 SAMPLE SIZE CALCULATION

We refer to the study protocol for complete details on sample size calculation.
For operational reasons, the study will recruit participants of all 103 ComBaCaL cohort villages. Based on a previous prevalence survey in the same two districts but different villages[1], we anticipate a total of 824 participants with uncontrolled arterial hypertension (TwiC 1) and 1030 participants with controlled arterial hypertension (TwiC 2). These numbers exceed, the required minimal sample sizes of 304 and 780 participants to detect superiority with a type I error of 0.025 and a statistical power of 80% for TwiC 1 and to detect non-inferiority with a type I error of 0.025 and a statistical power of 80% for TwiC 2.

## 4.6 RANDOMISATION PROCEDURE

All ComBaCaL cohort villages were randomized with a 1:1 ratio stratified by district (Butha-Buthe versus Mokhothlong) 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). Randomisation was conducted by a statistician not involved in the study.

## 4.7 SELECTION OF VILLAGES

Complete details on the selection of the ComBaCaL cohort villages are given in the protocol.

# 5 Quality Control and Validation Procedures

## 5.1 Data quality control and data validation procedures

All trial data and related cohort data collected in the villages are entered on spot using a tablet-based eHealth application with regular synchronization to a safe server hosted at the University Hospital Basel.

Cohort data are monitored on a regular basis by the principal investigator with additional data quality checks from the monitoring and quality team in Lesotho, and in close collaboration with the data manager in Switzerland. Participant records are checked for accuracy and consistency. Inconsistencies and unjustified missing data are flagged, and data queries are sent to the local team. All possible efforts are made to correct cohort data errors. In addition, the principal investigator visits field activities on a regular basis and provides direct supervision to ensure accuracy of data collection.

## 5.2 Randomisation Checks

Baseline imbalance between trial arms will be explored at the level of the villages, as well as the level of the participants. Beside participants 'characteristics such as sex, and age that are defined a priori for adjustment a priori for adjustment, we will compare the distribution of already in care for hypertension (only for TwiC 1), already in care for another chronic condition (HIV or diabetes), education status (secondary or higher *vs* lower), employment status (employed *vs* other), marital status and all the covariates listed as secondary outcome available at baseline across the two trial arms. No significance test for imbalance will be performed, following recommendations against this practice[2]. Baseline imbalance will be discussed from a clinical point of view and addressed in subsequent sensitivity analyses if considered appropriate.

## 5.3 Validation of statistical analysis

Analyses code used for the final analysis, including data cleaning, outcome derivation and other covariate analyses will be assessed and validated by a team member not involved in the study. Data will be shared on the Zenodo repository (www.zenodo.org) and statistical codes will be available upon reasonable request.

## 5.4 Automated checks

Data collected within the ComBCaL cohort through the ComBaCaL app undergo numerous built-in automated checks for inconsistency and missing data and flagging algorithms have been put in place. Complete details are given in the protocol.

# 6 Proposed Methodology

This section describes the methodology that shall be used when analysing and reporting the results for ComBaCaL arterial hypertension TwiC 1and ComBaCaL arterial hypertension TwiC 2.

## 6.1 BLINDING

Blinding is partial. Participants are not aware of the allocation: participants enrolled in the control villages are not aware of the intervention being implemented in other villages and *vice versa*. However, due to the nature of the intervention, village health workers and participants are not blinded to the intervention offered in their village.

## 6.2 PLANNED INTERIM ANALYSES

No interim analysis is planned.

## 6.3 TRIGGER FOR THE FINAL ANALYSIS

The trigger for the final analysis of the study is when all enrolled participants have either received an endpoint assessment within the predefined 12 months window (300-420 days after enrolment) or have a documented reason for not receiving an endpoint assessment (death, transfer out, exclusion from the trial/cohort) or passed the endpoint window. Therefore, the trigger date will not exceed 420 days after the enrolment of the last participant. Date of enrolment is the date of blood pressure measurement that define eligibility to the trials.

## 6.4 PATIENT GROUPS FOR ANALYSIS

All primary endpoint analyses will be carried out following the intention to treat (ITT) principle. This will retain participants in their initially randomized cluster, irrespective of any protocol deviation.
Participants that die from traumatic and non-traumatic deaths, are pregnant, lost to follow-up, transferred to another village, refused outcome measurement, refused village health worker care, do not adhere to pharmacological treatment, or stop prescribed treatment will be handled according to Table 1, following strategies defined within the estimand framework. Resulting datasets will define the ITT set for analyses.

Table 1: Intercurrent events and handling strategies.

| **Intercurrent event** | **Action** | **Estimand framework strategy** | **Comment** |
|---|---|---|---|
| Traumatic death | Exclusion from analysis | Principal stratum strategy: estimand population is defined to include participants that do not die from a traumatic death | We expect a traumatic death rate of 1% |

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| Non traumatic death | Imputation of primary endpoint as uncontrolled blood pressure if non traumatic death (worst case outcome) | Composite strategy: non traumatic death is included in the endpoint definition as "uncontrolled blood pressure or dying from non-traumatic death" | Non traumatic deaths may be associated to a negative primary endpoint |
| Pregnancy | Exclusion from analysis | Principal stratum strategy: estimand population is defined to include participants that are not pregnant | Expected self-reported pregnancy rate of around 1%. Pregnant women cannot benefit from a village health worker-led intervention as they require follow-up including hypertension management from professional antenatal care services |
| Lost to follow-up/transfer | Imputation of primary endpoint as uncontrolled blood pressure if non traumatic death (worst case outcome) | Composite strategy: lost to follow-up/transfer are included in the endpoint definition as "uncontrolled blood pressure or lost to care" | Lost to follow-up and transfer are treated together as it is difficult to differentiate them consistently in the two study arms. If more than 10% of study participants are lost to follow-up or transferred, robustness of the results will be assessed in a sensitivity analysis that exclude these participants |
| Refused outcome measurement, while still in care | If on pharmacological treatment -> imputation as controlled blood pressure<br>If not on pharmacological treatment or unknown treatment status-> imputation | Missing data | If more than 10% of study participants refused outcome measurement, robustness of the results will be assessed in a sensitivity analysis that consider all missing outcomes due to measurement |

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|---|---|---|---|
| | as uncontrolled blood pressure | | refusal as uncontrolled blood pressure |
| Refused village health worker care in intervention arm | Analysis as randomized | Treatment policy strategy | Description of participants characteristics will be provided |
| Nonadherence to the prescribed pharmacological treatment | Analysis as randomized | Treatment policy strategy | Description of participants characteristics will be provided |
| Stop pharmacological treatment due to side effects | Analysis as randomized | Treatment policy strategy | Description of participants characteristics will be provided |

The designed trials are pragmatic and aim at assessing two models of care in a real-world setting. Hence, the ITT set is the primary analysis population of most. Full adherence to the received treatment is unlikely in a real-world setting and strict per-protocol analyses will not be done. However, we define a safety analysis set of people who have at least one post enrolment visit with the village health worker in the intervention arm and participants who have at least one post enrolment visit at the health center in the control arm and describe the pathway of participants throughout the study (how many remained village health worker care, for how long, how many had safety events while being in care at health center versus while being cared by the village health worker). This will provide a more conservative analysis that is particularly relevant for safety outcome and TwiC 2 (non-inferiority trial) with an estimate of the effect of the ComBaCaL intervention with regards to blood pressure control among a population that agreed to link to care. Reasons for non-adherence and non-uptake of the intervention will be reported, together with a comparison of baseline participants characteristics.

Participant flow diagram will be presented according to the CONSORT 2010 statement extended to cluster randomized trial[4]. The flowchart will summarize – by study arms - the number of participants eligible according to ComBaCaL cohort data and baseline assessment. We will also show the flow for each scheduled visits (6 and 12 months) and summarize reasons for exclusion from the ITT and safety analysis sets.

## 6.5 Definition of Protocol Deviations

We do not define protocol deviations. Deviation from prescribed antihypertensive treatment, prescribed dosage, adherence to treatment or lifestyle counselling and no-shows to regular check-ups are not considered as a protocol deviation; participants being entirely free of their choices. We follow a treatment policy strategy to evaluate the effect of our intervention as part of routine practice.

## 6.6 Definition of adherence to intervention

Non-adherence to specific components of our intervention, as well as intervention uptake will be assessed and described accordingly.
The trials aim at testing the effect of a model of care. Defining adherence to all elements that compose the intervention model of care is complex. Full adherence to a model of care such the one developed in our intervention is unlikely.

## 6.7 Levels of Significance, Multiplicity Adjustments

The sample size calculation was carried out using a one-sided Type I error rate of 0.025. Therefore, the analysis of the primary outcomes will be assessed using a one-tailed p-value and a significance threshold set at 0.025. The primary efficacy parameter (adjusted odds ratio) will be presented with 95% confidence intervals. This applies to both ComBaCaL arterial hypertension TwiC 1 and ComBaCaL arterial hypertension TwiC 2.

ComBaCaL arterial hypertension TwiC 1 and ComBaCaL arterial hypertension TwiC 2 are two separate trials conducted in parallel. Participation in the trials is mutually exclusive. Each trial has one primary outcome and no correction for multiple testing will be applied.

No formal testing will be done for secondary and exploratory outcomes. We will report adjusted effects of intervention as odds ratio (binary outcomes) or intervention effect (continuous outcomes), together with 95%C confidence intervals.

## 6.8 Adjustment for Covariates

Primary outcomes will be analysed using generalized logistic mixed effect models where intervention, stratification factors (district and access to health facilities,) as well as baseline characteristics sex, and age are fixed effects and villages are random effects.

Secondary outcomes -if binary or continuous- will be analysed using generalized logistic or linear mixed models, depending on the nature of the outcome. The same adjustment factors will be considered. Models for secondary outcomes will be further adjusted for baseline information when available.

## 6.9 Missing Data

Primary analyses are planned on the ITT set (see section 6.4 for handling missing outcomes). Stratification variables and participant characteristics used for adjustment are not expected to be missing.

## 6.10 Pre-planned Sensitivity Analyses/additional analyses

We will perform the following sensitivity analyses:
-Sensitivity to the definition of primary outcome
We will assess robustness of our primary analyses by dropping participants with imputed primary outcomes due to refusal of outcome measurement, while still in care (primarily imputed as controlled/uncontrolled if on pharmacological treatment or

not, respectively), and due to lost to follow-up/transfer (primarily imputed as uncontrolled outcome).
-Sensitivity to baseline participants characteristics imbalance
If imbalance among study arms is judged clinically meaningful regarding smoking status, marital status, and all covariates listed as secondary outcomes available at baseline, we will consider them as additional fixed effect in a sensitivity analysis.

Our primary analyses follow an intention to treat strategy which might underestimate the effect of really receiving the intervention. Further exploratory analysis of the primary outcomes is planned to estimate the complier average causal effect of treatment (CACE), using a two-stage regression approach where we first regress randomization (the instrumental variable) on a compliance indicator and use the predicted value as a predictor in the regression of our outcome of interest. Such analysis will be further developed in a separate document and might be part of an additional publication.

### 6.11 Pre-specified Subgroups Analysis

Exploratory subgroup analyses will be conducted on the following sub-populations:
-Exclusion of participants not eligible for pharmacological treatment by the village health workers in control and intervention arms (people requiring three or more antihypertensive drugs, people with hypertensive emergency or clinical alarm symptoms or with intolerance or contraindication against amlodipine or hydrochlorothiazide). These participants are referred to the health facility for prescription of medication but are assumed to still benefit from the intervention package through treatment support provided by the village health worker.
-Exclusion of participants on antihypertensive treatment with SBP<120 and DBP <70 at baseline. These participants are assumed to be over-treated.

We additionally plan exploratory pooled analyses from ComBaCaL arterial hypertension TwiC 1 and ComBaCaL arterial hypertension TwiC 2.

We will assess effect modification of treatment effect on the primary endpoint for some pre-defined subgroups. If the p-values of an interaction term between intervention and age, sex, on antiretroviral therapy, hard access to health facility, already in care for arterial hypertension (only TwiC 1), and newly diagnosed are found to be below 0.1[3], effect estimates will be summarized descriptively by clinically relevant subgroup categories. Since the study is not powered for subgroup analyses, no formal testing will be done.
Pre-specified subgroups and hypotheses are:

- Age. Hypothesis: older participants are less mobile and benefit relatively more from the intervention model than younger participants.
- Sex. Hypothesis: Different care seeking behavior between male and female participants may result in different effects of the care models offered
- On antiretroviral therapy. Hypothesis: Participants already on antiretroviral treatment benefit less from the community-based care model given that HIV care is not part of it and therefore they still require regular visits at the health facilities
- Hard access to health facility. Hypothesis: participants living in village with hard access to a health facility benefit more from a village health worker-led intervention
- Already in care for arterial hypertension (TwiC 1). Hypothesis: participants already in care at the facility (but uncontrolled) will respond differently to the community-based care model than newly diagnosed participants or participants with a known diagnosis but not in care.

- Newly diagnosed. Hypothesis: participants newly diagnosed benefit more from the intervention as linkage to care is expected to be higher in intervention villages, where treatment is offered directly after diagnosis

## 6.12 Definition and Derivation of variables

**Baseline**: date of blood pressure measurement at TwiC enrolment
**12 months follow-up**: 300-420 days from baseline
**6 months follow-up**: 150-240 days from baseline
**Blood pressure**: mean of the last two out of three consecutive blood pressure measurements at one minute intervals
**Arterial hypertension diagnosis**: yes if intake of antihypertensive medication or being newly diagnosed according to diagnostic algorithm (BP above 180/110 after repeated measurement on one day or BP above 140/90 on two different days), otherwise no
**Uncontrolled blood pressure**: yes if systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, otherwise no.
**Controlled blood pressure**: yes if systolic blood pressure <140 mmHg and diastolic blood pressure< 90 mmHg, otherwise no
**10-year risk for a fatal or non-fatal cardiovascular event:** score estimated using the WHO cardiovascular disease risk prediction tool for Southern Sub-Saharan Africa.
**Body mass index** (kg/m^2): mass(kg)/height(m)^2.
**Abdominal circumference** (cm): circumference measured using an appropriate tape placed midway between the iliac crest and the lowest rib and taken at the end of a normal expiration.
**Blood lipid status**: Total cholesterol (mmol/l), low-density lipoprotein (mmol/l), high-density lipoprotein (mmol/l), triglycerides (mmol/l), total cholesterol/high-density lipoprotein ratio
**Physical activity**: score in MET minutes per week, estimated using the International Physical Activity Questionnaire Short Form (IPAQ-SF).
**Dietary habits**: Index from principal component analysis of 10 questions on junk food consumption. Frequency and quantity of salt, fruit and vegetable consumption.
**Alcohol use**: frequency of alcohol consumption
**Tobacco use**: yes if self-reported tobacco consumption, otherwise no
**Linkage to care**: yes if on pharmacological treatment while was not on treatment at baseline, otherwise no.
**Engagement in care**: yes if reporting intake of antihypertensive medication as per prescription of a healthcare provider (village health worker or healthcare professional) or reaching treatment targets without intake of medication, otherwise no
**Serious Adverse Events**: any untoward medical occurrence including occurrences that are not necessarily caused by or related to the study procedures
**Adverse Events of Special Interest**: adverse events consistent with arterial hypertension complications, such as stroke, myocardial infarction, hypertensive emergency, new diagnosis of heart failure or chronic kidney disease, and adverse events probably related to intake of antihypertensive medication leading to discontinuation of the medication concerned.
**Adherence to antihypertensive treatment**: yes if adherence to prescribed treatment defined as "self-reported non-missing medication in the last four days", otherwise no.
**Quality of life**: score using EQ-5D-5L instrument
**Health beliefs:** score estimated using the Beliefs about Medicines Questionnaire adapted for people living with arterial hypertension
**Access to care**: yes if access to care defined as "no self-reported unmet access to health care provider when needed in the last 6 months", otherwise no.

**Access to medication:** yes if access to medication defined as "no self-reported difficulty in obtaining medication in general", otherwise no.
**Number of consultations:** self-reported number of health facility visits and number of village health workers visits (number of forms submitted per participant as each form corresponds to one visit)
**Drug treatment interruption**: yes if under antihypertensive treatment at baseline and stop treatment or interrupt treatment for more than three weeks or require a switch of drug treatment due to (perceived) adverse events, otherwise no
**Treatment target reached**: yes if controlled blood pressure and no intake of antihypertensive medication, otherwise no
**Eligibility to access lipid-lowering medication**: yes if no contraindications and history of stroke or myocardial infarction, having diabetes mellitus or chronic kidney disease or being 50 years or older and having one or both of the following risk factors: body mass index ≥ 30 kg/m2 , currently smoking, otherwise no
**Perception of risks, benefits and problems of community-based management of uncomplicated arterial hypertension by village health workers:** qualitative assessment
**Reasons for drug treatment interruption**: qualitative assessment
**10-year cardiovascular Globorisk risk score**: score estimated using the Globorisk score
**10-year cardiovascular Framingham Risk Score:** score estimated using the Framingham risk score
**Type and dosage of antidiabetic and lipid-lowering medications prescribed within intervention model of care:** multiple choice output
**Grade III hypertension**: yes if systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg, otherwise no

### 6.13 Specification and Estimation of Efficacy Parameters

Individual-level mixed logistic regression model analyses will be performed to estimate the participant average intervention effect through the regression coefficient of the fixed effect of our intervention θ. The primary analysis will be adjusted for stratification factors, as well as for sex, and age. This represents the population impact of switching from control to intervention. We will additionally present absolute risk differences with 95% confidence interval estimated using the fitted models and bootstrap methods.
For ComBaCaL arterial hypertension TwiC 1, superiority will be assessed by testing the null hypothesis Ho: $\log(\theta)\leq 0$ versus H1: $\log(\theta)>1$, using the one-sided Z-test/Wald test (θ being defined as the adjusted odds ratio of intervention versus control). Superiority will be declared if the one-tail p-value is below our predefined 0.025 significance level. Adjusted odds ratio of intervention will be reported with 95% confidence interval, as well as unadjusted odds ratio for intervention.
For ComBaCaL arterial hypertension TwiC 2, non-inferiority margin was set to an OR=0.58 for the intervention. This corresponds to a maximal 10% acceptable reduction in reaching the primary outcome for the intervention for an hypothesized 80% controlled blood pressure in the control group. Non-inferiority of intervention will be assessed by testing the null hypothesis Ho: $\log(\theta)\leq\log(0.58)$ versus H1: $\log(\theta)>\log(0.58)$, using the one-sided Z-test. Non-inferiority will be declared if the one-tail p-value is below the predefined 0.025 significance. Adjusted odds ratio of intervention will be reported with 95% confidence interval, as well as unadjusted odds ratio for intervention.
All model parameters will be presented adjusted for pre-specified variables with 95% confidence intervals, as well as unadjusted for comparison. If adjusted and unadjusted estimates differ, effects of adjusting factors will be discussed consequently. In case the number of prespecified model parameter do not satisfy the common rule of thumb of one parameter in ten events for the analyses involving logistic regression, we will present

unadjusted odds ratios with 95% confidence intervals. Intraclass correlation coefficient will also be reported for each model.

Analyses of secondary outcomes will follow the same procedure using mixed effect logistic or linear regression, depending on the nature of the outcome. Serious adverse events, adverse events of special interest and adherence to antihypertensive treatment will however be purely descriptive. Exploratory outcomes will also be analyzed descriptively. Methods used for analyses are summarized in Table 2.

**Table 2: Methods summary for primary, secondary and exploratory outcomes analyses**

| Outcome Variable | Efficacy Parameter θ | Methods | Comments |
|---|---|---|---|
| **Primary outcome** | | | |
| Blood pressure controlled | Odds ratio | Mixed effect logistic regression model* | ComBaCaL arterial hypertension TwiC 1. Superiority will be assessed by testing the null hypothesis Ho: $\log(\theta)\leq 0$ *vs* $H_1$: $\log(\theta)>1$<br><br>ComBaCaL arterial hypertension TwiC 2. Non inferiority margin is set to an OR=0.58. Non-inferiority will be assessed by testing the null hypothesis Ho: $\log(\theta)\leq\log(0.58)$ *vs* $H_1$: $\log(\theta)>\log(0.58)$ |
| **Secondary outcomes** | | | |
| 10-year risk for a fatal or non-fatal cardiovascular event | Mean | Mixed effect linear regression model** | Adjusted and unadjusted effect with 95% confidence intervals |
| Body mass index | Mean | Mixed effect linear regression model** | Adjusted and unadjusted effect with 95% confidence intervals |
| Abdominal circumference | Mean | Mixed effect linear regression model** | Adjusted and unadjusted effect with 95% confidence intervals. |
| Total cholesterol/low-density lipoprotein/high-density lipoprotein/triglycerides/total cholesterol/high-density lipoprotein ratio | Mean | Mixed effect linear regression model** | Adjusted and unadjusted odds ratio with 95% confidence intervals |
| Physical activity | Mean | Mixed effect linear regression model** | Adjusted and unadjusted effect |

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| | | | with 95% confidence intervals. |
| Dietary habits index | Mean | Mixed effect linear regression model** | Adjusted and unadjusted effect with 95% confidence intervals. |
| Alcohol use | Mean | Mixed effect linear regression model** | Adjusted and unadjusted effect with 95% confidence intervals. |
| Tobacco use | Odds ratio | Mixed effect logistic regression model** | Adjusted and unadjusted effect with 95% confidence intervals |
| Linkage to care | Odds ratio | Mixed effect logistic regression model** | Adjusted and unadjusted effect with 95% confidence intervals |
| Engagement in care | Odds ratio | Mixed effect logistic regression model** | Adjusted and unadjusted effect with 95% confidence intervals |
| Serious Adverse Events | - | Purely descriptive by treatment arm and overall | Frequency of counts and percentages |
| Adverse events of special interest | - | Purely descriptive by treatment arm and overall | Frequency of counts and percentages |
| Adherence to antihypertensive treatment | - | Purely descriptive by treatment arm and overall | Frequency of counts and percentages |
| **Exploratory outcomes** | | | |
| Quality of life | - | Purely descriptive by treatment arm and overall | Mean score with 95% confidence intervals/median with interquartile range |
| Health beliefs: | - | Purely descriptive by treatment arm and overall | Mean score with 95% confidence intervals/median with interquartile range |
| Access to care | - | Purely descriptive by treatment arm and overall | Percentage with 95% confidence interval |
| Access to medication | - | Purely descriptive by treatment arm and overall | Percentage with 95% confidence interval |
| Number of consultations | - | Purely descriptive by treatment arm and overall | Mean with 95% confidence intervals/median with interquartile range |
| Drug treatment interruption | - | Purely descriptive by treatment arm and overall | Percentage with 95% confidence interval |

| | | | |
|---|---|---|---|
| Treatment target reached | - | Purely descriptive by treatment arm and overall | Percentage with 95% confidence interval |
| Eligibility to access lipid-lowering medication | - | Purely descriptive by treatment arm and overall | Percentage with 95% confidence interval |
| Perception of risks, benefits and problems of community-based management of uncomplicated arterial hypertension by village health workers | - | Purely descriptive by treatment arm and overall | Frequency and percentage of main responses |
| Reasons for drug treatment interruption | - | Purely descriptive by treatment arm and overall | Frequency and percentage of main responses |
| Health system costs and individual costs | - | To be defined | Cost analysis plan will be developed in separate documents and is planned to be presented as an additional publication |
| 10-year cardiovascular Globorisk risk score | - | Purely descriptive by treatment arm and overall | Mean score and change in score from baseline with 95% confidence intervals/median with interquartile range |
| 10-year cardiovascular Framingham Risk Score | - | Purely descriptive by treatment arm and overall | Mean score and change in score from baseline with 95% confidence intervals/median with interquartile range |
| Type and dosage of antihypertensive and lipid-lowering medications prescribed within intervention model of care | - | Purely descriptive by treatment arm and overall | Frequency and percentage of main responses |
| Grade III hypertension | - | Purely descriptive by treatment arm and overall | Percentage with 95% confidence interval |

* Models are adjusted for stratification factors (district and access to health facilities), age and sex; random effects are the villages (clusters).
** Models are adjusted for stratification factors (district and access to health facilities), age, sex and baseline outcome if measured; random effects are the villages (clusters).

### 6.14 TEST OF ASSUMPTIONS, ACTIONS TO BE TAKEN

Generalized logistic mixed models give equal weights to each participants. We assume that cluster size is non informative in this study.

### 6.15 Statistical Software

Statistical Analysis will be performed using the standard statistical packages R. The software and the version used for performing the analysis will be clearly mentioned in each output produced.

## 7 References

### 7.1 SOPs, Trial Specific Documents

Gerber, F et al. 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) *submitted to Trials*

### 7.2 External References

1 González Fernández, L et al (2024). Prevalence and determinants of cardiovascular risk factors in Lesotho: a population-based survey. *International Health* 16(3); 313–324

2 CPMP. Points to consider on adjustment for baseline covariates (CPMP/EWP/2863/99). London: EMEA; 2003.

3 Schandelmaier, S et al (2020). A New Instrument to Assess the Credibility of Effect Modification Analyses (ICEMAN) in Randomized Controlled Trials and Meta-Analyses. *CMAJ* 192(32)

4 Campbell, MK et al (2012). Consort 2010 statement: extension to cluster randomised trials. *BMJ* 345.

## STATISTICAL ANALYSIS *PLAN* SIGN-OFF SHEET

**This confirms approval of the Statistical Analysis Plan for ComBaCaL TwiC 1 & TwiC 2**

### Trial statistician

Name and affiliation: Frédérique Chammartin, Division of Clinical Epidemiology, University and University Hospital Basel

Signature: DocuSigned by: F. Chammartin 0E09BF2613A14B1...

Date: 31.05.2024 | 13:03 CEST

### Principal Investigator

Name and affiliation: Prof Niklaus D. Labhardt, Division of Clinical Epidemiology, University and University Hospital Basel

Signature: DocuSigned by: Niklaus Labhardt D61BC2E808E04F8...

Date: 31.05.2024 | 14:46 MESZ