Community-based type 2 diabetes care by lay village health workers in rural Lesotho (T2D TwiC)

Trial registration: ClinicalTrials.gov, NCT05743387

Protocol Version: v.1.1

Statistical Analysis Plan

Date Prepared: 21/11/2024

Version: v.1.1

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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 type 2 diabetes care by lay village health workers in rural Lesotho T2D TwiC. The planned analysis detailed in this document complies with the "Community-based type 2 diabetes care by lay village health workers in rural Lesotho: protocol for a cluster-randomized cohort study (ComBaCaL T2D TwiC) "[1].

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 important revision history of this document.

Document history summary:

Statistical Analysis Plan Version	Protocol Version	Section number(s) changed	Description of changes	Date Implemented
1.1	1.1	NA	NA	13.11.2024

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 study protocol might be referenced for a full description.

Title:	Community-based type 2 diabetes care by lay village health workers in rural Lesotho T2D TwiC
Design:	1:1 cluster-randomized, open-label trial nested within the ComBaCaL cohort study according to the TwiCs design
Expected Number of Participants:	240 participants across 100 clusters (120 per study arm)
Number of Sites:	103 ComBaCaL cohort villages

Study Duration:	Enrolment started on May 13, 2023. Enrolment stopped on January 31, 2024. Follow-up duration is 12 months (window 300-420 days) and will be completed by March 26, 2025.
Study population:	All adult and non-pregnant ComBaCaL cohort participants from the 103 ComBaCaL villages living with type 2 diabetes (defined as reporting intake of antidiabetic medication or being newly diagnosed during screening via standard diagnostic algorithm) were eligible for participation, included and followed up. However, the primary analysis set -on which the power calculation is based- includes only participants living with uncomplicated, uncontrolled (fasting blood glucose level >=7 mmol/l) type 2 diabetes.
Interventions:	Participants living in villages randomized to the <u>control arm</u> will follow the standard of care in the ComBaCaL cohort study. Participants diagnosed with type 2 diabetes by their Village Health Worker will be referred to health facility for follow-up and care. No prescription/provision of antidiabetic or lipid-lowering medication or treatment support will be provided. Participants will be followed-up after six- and 12-months including assessment of diabetes treatment and control status with referral to health facility if required. Participants living in villages randomized to the <u>intervention arm</u> will benefit from a community-based type 2 diabetes care package delivered by the village health worker including first-line antidiabetic treatment (metformin) and lipid-lowering treatment (atorvastatin) for uncomplicated type 2 diabetes patients and treatment support and regular check-ups for patients with complicated type 2 diabetes at community-level. Follow-up visits are scheduled according to the clinical need of participants, including the six- and 12-months assessments.
Endpoints:	<u>Primary</u> • Glycated haemoglobin (HbA1c) 12 months after enrolment. <u>Secondary</u> • 10-year CVD risk estimated using the WHO CVD risk prediction tool six- and 12-months after enrolment. • HbA1c six months after enrolment. • Fasting blood glucose six- and 12-months after enrolment. • HbA1c below 8% six- and 12-months after enrolment • Fasting blood glucose below 7 mmol/l six- and 12-months after enrolment. • Cardiovascular disease risk factors: smoking status, Body mass index, abdominal circumference, blood lipid status, blood pressure, and physical activity six- and 12-months after enrolment. • Linkage to care: proportion of participants that initiated pharmacological antidiabetic treatment six- and 12-months after enrolment among participants not taking treatment at enrolment.

	• Engagement in care: proportion of participants 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 12-months after enrolment or reaching treatment targets without intake of medication. • Self-reported adherence to antidiabetic treatment six- and 12-months after enrolment. • Occurrence of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) within six- and 12-months after enrolment. <u>Exploratory</u> • Dietary habits • Number of consultations at health facility and with the VHW at six- and 12-months follow-up. • 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). • Percentage stopping treatment or interrupting treatment for more than 3 weeks or required to switch due to perceived adverse events at six- and 12-months follow-up. • Percentage of participants reaching treatment target (fasting blood glucose <7 mmol/l) and reporting no intake of medication in the 2 weeks prior assessment at six- and 12-months. • Perception of risk, benefits, and problems of community-based management of uncomplicated type 2 diabetes by villages health workers among participants, village health workers and involved health care professionals. • Reasons for stopping or interrupting antidiabetic treatment, as well as reason for switching to health facility-based treatment within the course of the trial in intervention arm. • Cost of intervention at the level of the health system and at individual level for the management of their condition within six- and 12-months follow-up. • 10-year cardiovascular disease risk score using the Framingham risk score and the Globorisk score at six- and 12-months follow-up. • Quality of life using the EQ-5D5L instrument at 12 months follow-up at 12 months follow-up • Health beliefs using the Beliefs about Medicines Questionnaire adapted for people living with type 2 diabetes. • Diabetes distress using the five-item version of the "Problem Areas in Diabetes" (PAID-5) scale. • Self-reported access to care.

	• Self-reported access to medication. • Type and dosage of antidiabetic and lipid-lowering medications prescribed at 6 months and 12 months follow-up.

4 TRIAL OVERVIEW

4.1 BACKGROUND AND RATIONALE

Type 2 diabetes prevalence is increasing mainly due to population ageing and lifestyles changes with decreasing levels of physical activity, high calory intake and associated obesity. Undetected and untreated diabetes risk is high in low and middle-income countries. Task-shifting to village health workers and use of digital clinical decision support has the potential to improve the diabetes care cascade. Randomized evidence regarding the effectiveness of comprehensive village health worker-led diabetes care models, where village health workers administer first line anti-diabetes medications and address cardiovascular risk factors is needed to guide future development of community-based diabetes care models in Lesotho and similar settings. We refer to the study protocol for more details.

4.2 TRIAL DESIGN AND INTERVENTION

This is a 1:1 cluster-randomized, open-label trials within the ComBaCaL cohort study according to the TwiCs design. The TwiCs design requires prior consent of cohort participants for randomization. Participants allocated to the control arm are not informed of their participation in the trial and follow routine cohort procedures. The intervention (community-based management of type 2 diabetes 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 primary objective of this study is to test superiority of the proposed village health worker model of care to the routine ComBaCaL cohort care in terms of HbA1c level at 12 months follow-up among adults with uncontrolled and uncomplicated type 2 diabetes.

4.4 ELIGIBILITY CRITERIA

Inclusion Criteria
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), living with a type 2 diabetes (reporting intake of antidiabetic medication or being newly diagnosed during screening via standard diagnostic algorithm).
The primary analysis is restricted to individuals with uncontrolled diabetes (fasting blood glucose level >=7 mmol/l).

Exclusion Criteria
Self-reported pregnancy at baseline and known type 1diabetes mellitus.

4.5 SAMPLE SIZE CALCULATION

We refer to the study protocol for complete details on sample size calculation.
In brief, we aim at recruiting 240 participants across 103 villages (120 across 51-52 villages per study arm) for the primary analysis to detect superiority of our intervention with a type I error of 0.05 and a statistical power of 80%., assuming a minimum detectable difference in HbA1c between study arms of 0.6%, and an intra-cluster correlation of 0.015. This calculation anticipates an attrition rate of 20%.
For operational reason, we will recruit all eligible participants in the ComBaCaL villages. An overview of sample size required in relation to different statistical power and type I error is given in Figure 1.

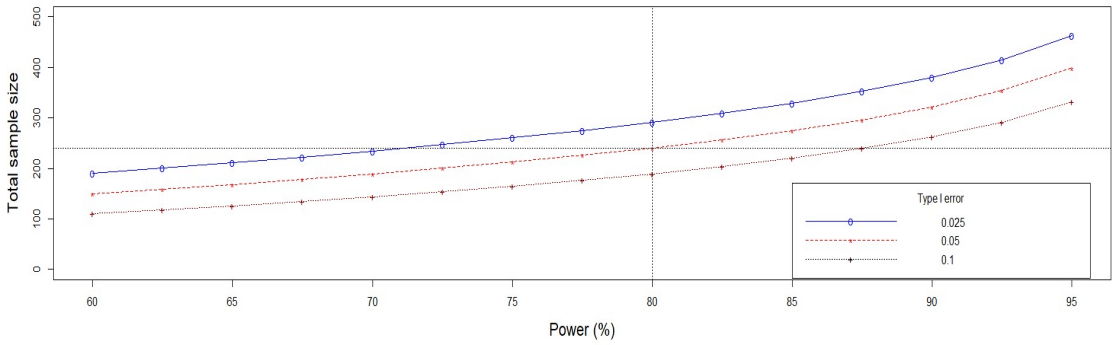

Figure 1: Sample size calculation for the primary analysis population based on different statistical powers and type I errors.

4.6 RANDOMISATION PROCEDURE

All 103 ComBaCaL cohort villages were randomized with a 1:1 ratio 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). 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 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.

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 for follow-up with the Village Health Workers and correction if needed. 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. At participant level, we will compare sex, and age that are defined a priori for adjustment, and the distribution of already in care for diabetes, and the relevant covariates listed as secondary outcome available at baseline across the two trial arms. At cluster level, we will compare cluster size, number of patients living with type 2 diabetes (controlled and uncontrolled), and stratification variables for randomization district and access to health facilities. 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 reviewed according to a four eyes principle. 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 T2D TwiC.

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*. Village health workers and participants are not blinded to the intervention (everyone knows what they get).

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, withdrawal) 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 when a participant is diagnosed with type 2 diabetes by the VHW during screening, defined as reporting intake of antidiabetic medication or being newly diagnosed according to the diagnostic algorithm.

6.4 PATIENT GROUPS FOR ANALYSIS

The primary endpoint analysis 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 were found ineligible after enrolment, will be reported as post-randomization exclusions and not be considered for the analysis.
Participants that die, are pregnant, transferred to another village or lost to follow-up, refused outcome measurement, refused village health worker care 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**
Death	Exclusion from analysis	Principal stratum strategy: estimand population is defined to include participants that do not die	
Pregnancy	Exclusion from analysis	Principal stratum strategy: estimand population is defined to include participants that are not pregnant	Pregnant women cannot benefit from a village health worker-led intervention as they require follow-up from professional antenatal care services

Transfer (moving out of the study village)	Exclusion from analysis	Principal stratum strategy: estimand population is defined to include participants that are not lost or transferred	
Refused HbA1c assessment while still being in the village, withdraw of ComBaCaL cohort consent or missing data	Estimated from a linear model fitted on full dataset based on 12-months FBG (missing, low <5.6 mmol/l, moderate 5.6-7 mmol/l, high ≥7 mmol/l) and baseline characteristics	Missing data	Robustness of the results will be assessed in a sensitivity analysis that drops participants with missing data
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 a model of care in a real-world setting. Hence, the ITT set is the primary analysis population of interest. Full adherence to the received intervention is unlikely in a real-world setting and strict per-protocol analyses will not be done. 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 [3]. 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 (six- and 12-months) and summarize reasons for exclusion from the analysis.

6.5 Definition of Protocol Deviations

Deviation from prescribed antidiabetic treatment, prescribed dosage, adherence to treatment or lifestyle counselling and no-shows to regular check-ups are not considered as a protocol deviation. Table 1 outlines how intercurrent events are addressed. Overall, 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 trial aims 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 the model of care tested in this trial is unlikely.

6.7 Levels of Significance

The sample size calculation was carried out using a two-sided Type I error rate of 0.05. Therefore, the analysis of the primary outcomes will be assessed using a two-tailed p-value and a significance threshold set at 0.05. The primary efficacy parameter (adjusted regression coefficient for intervention) will be presented with 95% confidence intervals.

No formal testing will be done for secondary outcomes. We will report adjusted effects of intervention as odds ratio (binary outcomes) or magnitude of change (regression coefficient for continuous outcomes), together with 95% confidence intervals.

6.8 Adjustment for Covariates

Primary outcomes will be analysed using generalized linear mixed effect models where intervention, stratification factors (district and access to health facilities,) as well as baseline characteristics sex, and age, and HbA1c are fixed effects and villages are random effects. Missing baseline HbA1c will be estimated from a linear model fitted on full dataset based on baseline FBG (missing, low <5.6 mmol/l, moderate 5.6-7 mmol/l, high ≥7 mmol/l) and baseline characteristics.

Secondary outcomes -if binary or continuous- will be analysed using generalized logistic or linear mixed models, depending on the nature of the outcome. Adjustment factors district, access to health facility, age and sex 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, except for baseline HbA1c that will be estimated from a linear model fitted on full dataset based on baseline FBG (missing, low <5.6 mmol/l, moderate 5.6-7 mmol/l, high ≥7 mmol/l) and baseline characteristics.

6.10 PRE-PLANNED SENSITIVITY ANALYSES/ADDITIONAL ANALYSES

We will perform the following sensitivity analyses:
-Sensitivity to baseline participants characteristics imbalance
If imbalance among study arms is judged clinically meaningful regarding any covariate, we will consider them as additional fixed effect in a sensitivity analysis.
-Sensitivity to inclusion criteria
Inclusion criteria for the primary analysis population include uncomplicated (no antidiabetic treatment or only one class of oral antidiabetic treatment and not meeting the criteria for direct referral (FBG ≥14 mmol/l or RBG ≥16.7 mmol/l or having polyuria, polydipsia and weight loss)), uncontrolled (FBG ≥7 mmol/l) diabetes. We will assess robustness of our result for both primary and secondary analyses by only considering trial participants with 1) uncontrolled, uncomplicated (FBG ≥7 mmol/l) diabetes and a baseline HbA1c ≥ 6.5%, 2) all study participants independent of uncontrolled/controlled or uncomplicated/complicated diabetes and a baseline HbA1c ≥ 6.5%, 3) all study participants independent of uncontrolled/controlled, uncomplicated/complicated diabetes and independent of baseline HbA1c
-Sensitivity to extrapolation of missing data
We will perform a sensitivity analysis by excluding from the analysis participants with missing HbA1c (baseline and 12-months) to assess robustness to extrapolation from FBG.
-Sensitivity to exclusion
We will perform a sensitivity analysis by imputing HbA1c 12-months outcome of participants that experience an intercurrent event pregnancy or transfer

Our primary analysis follows 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

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 (continuous), sex, hard access to health facility, or already in care for diabetes and newly diagnosed is found to be below 0.1 [4], effect estimates will be summarized descriptively by clinically relevant subgroup categories. The study is not powered for any treatment-covariate interaction.
Pre-specified subgroups and hypotheses are:

- Age (continuous). Hypothesis: older participants are less mobile and benefit relatively more from the intervention model than younger participants.
- Sex (women vs men). Hypothesis: Different care seeking behavior between male and female participants may result in different effects of the model of care offered (hypothesis direction unclear).
- Access to health facility (easy versus hard). Hypothesis: participants living in villages with hard access to a health facility benefit more from a village health worker-led intervention.

- Diagnosis status (newly diagnosed for diabetes versus already in care for diabetes (but uncontrolled)). Hypothesis: participants newly diagnosed benefit more from the intervention as we expect a higher effect through improved linkage to care in this subgroup versus the subgroup of people already living with diabetes and "only" benefitting from improved treatment monitoring.

6.12 Definition and Derivation of variables

Baseline: date of HbA1c measurement at TwiC assessment.
12 months follow-up: 300-420 days from baseline.
6 months follow-up: 150-240 days from baseline.
HbA1c: Glycated haemoglobin level in % measured on site on capillary blood glucose using the A1CNow + Professional system.
10-year cardiovascular diseases risk: score estimated using the WHO cardiovascular disease risk prediction tool for Southern Sub-Saharan Africa.
Fasting blood glucose: capillary blood glucose level in mmol/l measured on site after a minimum of 8 hours without calory intake.
Smoking status: yes if self-reported smoking tobacco consumption, otherwise no
Body mass index (kg/m^2): mass(kg)/height(m)^2.
Abdominal circumference: circumference in cm 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) .
Blood pressure: systolic and diastolic blood pressure in mmHg
Dietary habits: Index from principal component analysis of questions on junk food consumption. Frequency and quantity of fruit and vegetable consumptions.
Physical activity number of metabolic equivalent of task (METs)
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 antidiabetic medication as per prescription of a healthcare provider (village health worker or healthcare professional) or reaching treatment targets without intake of medication, otherwise no.
Self-reported adherence to antidiabetic medication: yes if "self-reported non-missing medication in the last four days", otherwise no.
Serious adverse events: any untoward medical occurrence including occurrences that are not necessarily caused by or related to the study procedure.
Adverse events of special interest: adverse events consistent with diabetes complications, such as myocardial infraction, stroke, symptomatic heart failure, chronic kidney disease, blindness, severe vision impairment, or intolerant reaction against antidiabetic medication like allergic reaction, drug interaction or rare severe side effect.
Number of consultations at health facility: self-reported number of health facility visits.
Stopping treatment or interrupting treatment for more than 3 weeks, or required to switch due to perceived adverse events: yes if under 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.
Reaching treatment target without intake of antidiabetic medication: yes if fasting blood glucose <7 mmol/l and self-reporting of no antidiabetic medication two weeks prior assessment, otherwise no.
On lipid-lowering medication: yes if self-reported intake of lipid-lowering medication, otherwise no.

Perception of risks, benefits and problems of community-based management of uncomplicated diabetes by participants, village health workers and involved health care professionals: qualitative assessment.
Reasons for stopping or interrupting antidiabetic treatment, as well as reason for switching to health facility-based treatment within the course of the trial: qualitative assessment.
10-year cardiovascular Framingham risk score: score estimated using the Framingham risk score.
10-year cardiovascular disease Globorisk risk score: score estimated using the Globorisk score.
Quality of life: score calculated using the EQ-5D5L questionnaire.
Health beliefs: score calculated using the Beliefs about Medicines Questionnaire adapted for people living with type 2 diabetes.
Diabetes distress: score calculated using the 5-item version of the "Problem Areas in Diabetes" (PAID-5) questionnaire.
Access to care: yes if access to care defined as "no self-reported unmet access to health care provided when needed in the last six months", otherwise no.
Access to medication: yes if access to medication defined as "no self-reported unmet access to medication when needed in the last six months", otherwise no.
Type and dosage of antidiabetic and lipid-lowering medications prescribed: qualitative assessment.

6.13 Specification and Estimation of Efficacy Parameters

Individual-level mixed linear 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, age, and baseline HbA1c. This represents the average difference in HbA1c of switching from control to intervention when controlling for the aforementioned covariates. We will additionally present absolute differences with 95% confidence interval estimated using the fitted models and bootstrap methods.
Superiority will be assessed by testing the null hypothesis Ho: $\theta \leq 0$ versus H1: $\theta > 0$, using the two-sided Z-test/Wald test (θ being defined as the adjusted regression coefficient of intervention). Superiority will be declared if the one-tail p-value is below our predefined 0.05 significance level. Estimated effect of intervention will be reported with 95% confidence interval, as well as unadjusted effect 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.

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. Methods used for analyses are summarized in Table 2.

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

Outcome Variable	Efficacy Parameter θ	Methods	Comments
Primary outcome			
HbA1c	Mean	Mixed effect linear regression model*	Superiority will be assessed by testing

			the null hypothesis Ho: $\theta \leq 0$ *vs* H_1: $\theta > 1$
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
Fasting blood glucose	Mean	Mixed effect linear regression model*	Adjusted and unadjusted effect with 95% confidence intervals
Smoking	Odds ratio	Mixed effect logistic regression model*	Adjusted and unadjusted effect with 95% confidence intervals
Blood pressure	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 / high-density lipoprotein ratio	Mean	Mixed effect linear regression model*	Adjusted and unadjusted effect with 95% confidence intervals
Physical activity	Mean	Mixed effect linear 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 antidiabetic treatment	-	Purely descriptive by treatment arm and overall	Frequency of counts and percentages
Exploratory outcomes			
Dietary habits	-	Purely descriptive by treatment arm and overall	Mean number with 95% confidence intervals/median

			with interquartile range
Number of consultations at health facility	-	Purely descriptive by treatment arm and overall	Mean number with 95% confidence intervals/median with interquartile range
Stopping treatment or interrupting treatment for more than 3 weeks, or required to switch due to perceived adverse events	-	Purely descriptive by treatment arm and overall	Percentage with 95% confidence intervals/median with interquartile range
Reaching treatment target (fasting blood glucose <7 mmol/l) and reporting no intake of medication in the 2 weeks prior assessment	-	Purely descriptive by treatment arm and overall	Percentage with 95% confidence interval
On 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
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
Quality of life	-	Purely descriptive by treatment arm and overall	Mean score and change in score from baseline with 95% confidence intervals/median with interquartile range

Health beliefs	-	Purely descriptive by treatment arm and overall	Mean score and change in score from baseline with 95% confidence intervals/median with interquartile range
Diabetes distress	-	Purely descriptive by treatment arm and overall	Mean score and change in score from baseline 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
Type and dosage of antidiabetic and lipid lowering medication	-	Purely descriptive by treatment arm and overall	Frequency and percentage of main responses

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

6.14 Test of Assumptions, Actions to be taken

Generalized linear mixed models give equal weights to each participants. We assume that cluster size is non informative since we will have relatively few individuals per cluster and more than 100 clusters overall.

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 type 2 diabetes care by lay village health workers in rural Lesotho: protocol for a cluster-randomized trial within the ComBaCaL cohort study (ComBaCaL T2D TwiC). Trials 24(1): 688.

7.2 External References

1 Gerber, F et al (2023). Community-based type 2 diabetes care by lay village health workers in rural Lesotho: protocol for a cluster-randomized trial within the ComBaCaL cohort study (ComBaCaL T2D TwiC). *Trials* 24(1): 688.

2 The European Agency for the Evaluation of Medicinal Products - Committee for proprietary medicinal products (CPMP). Points to consider on adjustment for baseline covariates (CPMP/EWP/2863/99). London: EMEA; 2003.

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

4 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)

STATISTICAL ANALYSIS *PLAN* SIGN-OFF SHEET

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

Trial statistician

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Date _ _ / _ _ / _ _ _ _

Retain Original Copy of Report & Sign-off sheet in appropriate sections of Statistics File. Keep a scanned copy of each in corresponding electronic folder.