Study Protocol

Community-based, eHealth supported 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)

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

Study acronym/ID	ComBaCaL T2D TwiC		
Protocol Version Nr	1.2	**Date**	07.06.2025
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Funding Agency	Swiss Development Cooperation, World Diabetes Foundation		

1 GENERAL INFORMATION

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

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

1.2 Signatures

Study Title: "Community-based, eHealth supported 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)"

The following project leaders have approved the protocol, version 1.2, dated 07.06.2025, and confirm hereby to conduct the project according to the current version of the Declaration of Helsinki as well as all national legal requirements and guidelines as applicable.

Principal Investigator:

- I have read this protocol, version 1.2, dated 07.06.2025, and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.
- I will ensure that all individuals and parties contributing to this study are qualified and I will implement procedures to ensure integrity of study tasks and data.
- I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed and trained regarding their activities within the study conduct.
- I will use only approved informed consent forms and will fulfil all responsibilities for submitting pertinent information to the Independent Ethics Committees responsible for this study.
- It is understood that this protocol will not be disclosed to others without prior written authorisation from the Project Leader or Sponsor, except where required by applicable local laws

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1.3 Abbreviations / Glossary of terms

AE	Adverse event
AESI	Adverse event of special interest
aHT	Arterial hypertension
BMI	Body mass index
BG	Blood glucose
BP	Blood pressure
CC-VHW	Chronic care village health worker
CC nurse	Chronic care nurse
ComBaCaL	Community-Based Chronic Disease Care Lesotho
CVD	Cardiovascular disease
CVDRF	Cardiovascular disease risk factor
DHMT	District Health Management Team
EKNZ	Ethics Committee of Northern and Central Switzerland
FBG	Fasting blood glucose
HbA1c	Glycated haemoglobin
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICHOM	International Consortium for Health Outcomes Measurement
IEC	Independent Ethics Committee
IT	Information technology
ITT	Intention-to-treat
LHW	Lay healthcare worker
LMICs	Low- and middle-income countries
MoH	Ministry of Health
NCD	Non-communicable disease
NHREC	National Health Research Ethics Council
PP	Per protocol
RBG	Random blood glucose
SAE	Serious adverse event
SAP	Statistical analysis plan
T2D	Type 2 diabetes mellitus
TwiC	Trial within cohort
VHW	Village health worker
WHO	World Health Organization

2 SYNOPSIS

Project Leaders	Prof. Dr. Niklaus Labhardt
Study Title	Community-based, eHealth supported type 2 diabetes care by lay village health workers in rural Lesotho: Protocol for a cluster-randomized trial within the ComBaCaL cohort study
Short Title/Study ID	ComBaCaL T2D TwiC
Protocol Version and Date	Version 1.2, 07.06.2025
Study Category with Rationale	Implementation research trial Risk category A
Background and Rationale	Globally, 9.3% of the adult population or 436 million individuals were estimated to be living with diabetes in 2019. Until 2045 this number is expected to increase by more than 50% to over 700 million.[1,2] Four out of five people affected by diabetes are currently living in low- and middle-income countries (LMICs).[3] Over 90% of all diabetes cases are due to type 2 diabetes (T2D) which is also the main driver of the projected increase in overall diabetes cases[1]. The increase in T2D prevalence is caused by ageing populations and changing lifestyles with decreasing levels of physical activity, higher caloric diets and associated obesity.[4] Currently, only half of the people living with diabetes are aware of their high blood sugar levels and the associated health risks.[1,2] The risk for diabetes to remain undetected and untreated and therefore earlier complications is significantly higher in LMICs than in high-income countries.[3,5] At the same time, the management of diabetes complications is costly and not accessible in most LMICs in sub-Saharan Africa and elsewhere, therefore prevention via risk factor control and adequate antidiabetic treatment before onset of complications is essential.[6,7] Setting-specific, affordable and scalable solutions need to be developed as it is not possible to plainly reproduce strategies from high-income countries in resource-scarce settings[7]. Incorporating lay healthcare workers (LHWs) delivering education, screening and care-support at community-level is a promising approach to improve access to and outcomes of diabetes care in sub-Saharan Africa[8–10]. Many countries have established LHW systems, traditionally focusing on maternal and neonatal health and on communicable diseases, especially HIV/AIDS. In recent years however, increasing evidence has emerged showing a beneficial effect and high cost-effectiveness of LHW-based models on diseases outside this traditional scope, especially for non-communicable diseases (NCDs) such as diabetes and arterial hypertension (aHT)[9,11,12]. However, while screening, education and self-management support interventions by LHWs in the community have been tested successfully, it remains unclear whether such interventions are sufficiently effective to sustainably close the current treatment gap.[7] A study in South Africa exploring NCD screening by LHWs at community-level has shown a high proportion of newly detected T2D cases, who were referred to a health facility for follow-up care. However, only 29% of participants with elevated blood glucose (BG) during screening actually linked to facility-based care indicating limited effectiveness of community-based screening and linkage services.[13]

	In this trial embedded in the ComBaCaL (Community-based chronic disease care Lesotho) cohort, using the Trials within Cohorts (TwiCs) approach, we want to explore whether an LHW-led model could be capacitated to safely and effectively provide first-line management (including oral antidiabetic, lipid-lowering treatment and lifestyle counselling) at community-level. This TwiC has been developed based on a local NCD prevalence survey and burden assessment (NH-REC 130-2021), a scoping literature review[14], multiple workshops with different stakeholders in Lesotho and the ComBaCaL pilot cohort study (NH-REC 176-2021). In villages randomized to the intervention arm, lay Chronic Care Village Health Workers (CC-VHWs) operating within the existing Ministry of Health (MoH) village health worker system will be capacitated to screen for and diagnose T2D, to provide lifestyle counselling, to prescribe and to monitor first-line antidiabetic and lipid-lowering treatment for uncomplicated T2D and to provide treatment support for complicated T2D, supported by a tailored clinical decision support application (ComBaCaL app) in their villages. In villages randomized to the control arm, CC-VHWs will only screen for and diagnose T2D with subsequent standardized counselling and referral to the closest health facility for further care, but no village-based prescriptions or treatment support.
Objectives	**Primary objective** • To assess the effect of community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho on blood sugar control among adults with uncomplicated T2D and a fasting blood glucose (FBG) ≥7 mmol/l at baseline **Secondary objectives** • To assess the effect of community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho on blood sugar control in different secondary analysis populations (see definition in section “Analysis Sets”) • To assess the effect of CC-VHW led, eHealth supported T2D care on 10-year CVD risk using the WHO CVD risk prediction tool[15] • To assess the effect of CC-VHW led, eHealth supported T2D care on CVD risk factors including body-mass index (BMI), abdominal circumference, blood lipid status, tobacco use, physical activity and dietary habits • To assess the safety of CC-VHW led, eHealth supported T2D care • To assess the effect of CC-VHW led, eHealth supported T2D care on linkage and engagement in care and on adherence to treatment • To assess the sustained safety and feasibility of CC-VHW led, eHealth supported T2D care and sustained effect on reaching blood sugar control, 10-year CVD risk, CVD risk factors, linkage to care, engagement in care and adherence to treatment among adults with uncomplicated T2D and a FBG ≥7 mmol/l at baseline and in different secondary analysis populations (see definition in section “Analysis Sets”).
Hypothesis and estimand	Primary hypothesis: Community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho is safe and superior with regard to HbA1c levels twelve months after enrolment compared to facility-based T2D care among non-pregnant adults with uncomplicated uncontrolled T2D. Primary estimand: HbA1c reduction (mean difference) 12 months after enrolment between community-based, CC-VHW-led, eHealth supported T2D care versus facility-based T2D care, in non-pregnant adults with uncomplicated (no insulin, not more than one oral antidiabetic, no direct referral required) uncontrolled (FBG ≥ 7 mmol/l) T2D who are still alive and did not move out of their village, irrespective of the uptake of the intervention, T2D treatment, T2D treatment adherence and adverse events.

Endpoints	**Primary endpoint** • Mean HbA1c twelve months after enrolment **Secondary endpoints** • 10-year CVD risk estimated using the WHO CVD risk prediction tool[15,16] at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment • Mean HbA1c at six months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment • Mean FBG at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment • Proportion of participants with an HbA1c below 8% at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment • Proportion of participants with an FBG below 7 mmol/l at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment • CVD risk factors, such as smoking status, BMI, abdominal circumference, blood lipid status, blood pressure, dietary habits and physical activity at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment • Linkage to care: proportion of participants not taking treatment at enrolment who have initiated pharmacological antidiabetic treatment at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 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 (CC-VHW or healthcare professional) at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment or reaching treatment targets without intake of medication • Self-reported adherence to antidiabetic medication at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment • Occurrence of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) within six and twelve months, as well as at within subsequent time intervals during a total follow-up period of up to 48 months after enrolment The primary and secondary endpoints will first be assessed in the primary analysis set (see definition below), following the primary hypothesis and primary estimand. Secondly, the primary and secondary endpoints will be assessed in the three secondary analyses sets (see definition below).
Intervention	CC-VHWs are providing a T2D care package consisting of screening, diagnosis and counselling services as well as first-line antidiabetic treatment (metformin) and lipid-lowering treatment (atorvastatin) for uncomplicated T2D patients and treatment support and regular check-ups for patients with complicated T2D at community-level. CC-VHWs are equipped with a tablet where a dedicated application, the ComBaCaL app, guides them to provide the above-mentioned services. Appropriately trained, supervised and mentored by chronic care nurses (CC nurses) and guided by the ComBaCaL app they will follow-up persons with T2D to monitor adherence, life-style changes, treatment response and side-effects.

Control	Control villages will follow the standard of care in the ComBaCaL cohort study. CC-VHWs will also receive tablets with the ComBaCaL app installed. They are trained, supervised and equipped to screen and diagnose T2D with subsequent referral to facility-based follow-up and care. In control villages the ComBaCaL app supports clinical decision making and documentation for screening, diagnosis and referral, but not prescription/provision and monitoring of antidiabetic or lipid-lowering medication for uncomplicated T2D patients or treatment support for complicated T2D patients.
Study Design	We are conducting a cluster-randomized controlled trial nested within the ComBaCaL cohort study following a trial within cohort (TwiC) approach[17,18]. 50% of the villages being part of the overarching ComBaCaL cohort will be randomized stratified by district and access to health facility to receive the intervention as described above.
Eligibility criteria	**Inclusion criteria** - Participant of the ComBaCaL cohort study (signed informed consent available) - Aged 18 years or above - Living with T2D, defined as reporting intake of antidiabetic medication or being newly diagnosed during screening via standard diagnostic algorithm **Exclusion criteria** - Known type 1 diabetes mellitus - Reported pregnancy
Analysis sets	Primary analysis set: All study participants with uncomplicated, uncontrolled T2D at baseline, defined as: - Uncomplicated: o No treatment or uncomplicated treatment defined as taking only one class of oral antidiabetic drugs (i.e. metformin) o Not meeting criteria for direct referral, which are defined as: ▪ FBG > 14 mmol/l OR ▪ RBG > 16.7 mmol/l OR ▪ Having polyuria, polydipsia and weight loss - Uncontrolled: FBG ≥7 mmol/l Secondary analyses sets: a) Only study participants with uncontrolled, uncomplicated T2D and a baseline HbA1c 6.5% and above b) Only study participants with a baseline HbA1c 6.5% and above **c)** All study participants
Measurements and Procedures	Screening, enrolment, baseline and endpoint assessments will be conducted by CC-VHWs at community-level. We refer to the current version the "ComBaCaL cohort study protocol" for detailed information about the cohort set-up and procedures. In brief, CC-VHWs screen for and diagnose T2D via capillary blood glucose (BG) measurements, based on standardized algorithms encoded in the tablet-based ComBaCaL app. In villages not allocated to the TwiC intervention (control villages), participants diagnosed with T2D receive a standardized counselling by the CC-VHW and are referred to the closest health facility for initiation or continuation of antidiabetic treatment. In the randomly selected intervention villages, CC-VHWs will provide a T2D care package including life-style counselling and the offer of oral first-line antidiabetic (metformin) and lipid-lowering (statin) treatment for uncomplicated T2D and

	treatment support and monitoring for complicated T2D guided by the ComBaCaL app. Participants are free to accept or refuse the services offered by the CC-VHW at any time. Prior to implementation, CC-VHWs in intervention villages will receive trainings on the basic mechanisms of action, contraindications and potential side effects of the antidiabetic and lipid-lowering treatment used as well as on adherence counselling techniques, on the interpretation of BG values and on basic clinical examination skills for the recognition of possible adverse events. Direct guidance for treatment initiation, drug prescription, counselling and monitoring will be provided via the ComBaCaL app. All activities conducted by CC-VHWs in the communities, including counselling and drug prescription, will also be captured in the ComBaCaL app. Health care professionals and supervising study staff will monitor all activities in a web version of the app and will be intervening in case of missing data, non-adherence to the clinical algorithms, or unclear clinical conditions. The CC-VHWs may always request support by supervising health care professionals. In case of complicated disease, unclear diagnosis, or presence of clinical alarm signs or symptoms, participants will be referred immediately to the closest health facility for further investigation. Endpoint assessments after six and twelve months, as well as after subsequent timepoints over a total follow-up period of up to 48 months after enrolment, including HbA1c, blood lipid status and FBG measurements, capturing of possible SAEs and AESIs as well as administration of questionnaires on adherence and modifiable cardiovascular disease risk factors (CVDRFs) will be conducted by CC-VHWs in an identical manner in intervention and control villages and captured in the ComBaCaL app. If resources allow, certain endpoints (i.e. HbA1c) will be assessed by study personnel not involved in the care at village-level. In addition, questionnaires about participants' satisfaction and acceptability of the TwiC intervention will be administered and semi structured interviews with a selection of participants, CC-VHWs and involved health care professionals will be conducted to qualitatively explore perceived risks, benefits and problems of community-based T2D care.
Number of Participants with Rationale and Power Analysis	The ComBaCaL cohort will consist of inhabitants of around 100 (range 90-112) randomly selected villages in rural Lesotho. The estimated mean number of adult ComBaCaL participants per village is 100 resulting in an estimated 10'000 adult cohort participants. Sample size for the TwiC is calculated assuming an individual randomization inflated by a design effect that account for variation at cluster level, according to the code developed by Rotondi and Donner[19]. Based on preliminary results from an NCD prevalence survey in the region (NH-REC ID 139-2021), we expect the prevalence of T2D in the adult population in the rural setting in Lesotho to be around 4%, with about 60% of people living with T2D fulfilling the criteria for the primary analysis set (not pregnant, no type 1 diabetes mellitus, no complicated treatment, not meeting criteria for insulin treatment, FBG ≥7 mmol/l). Hence, considering an average cluster size of 100 adult inhabitants, the mean number of inhabitants eligible for the TwiC is 2.4 per village. We estimate an effect size of 0.6% HbA1c mean difference between the two groups after 12 months. Assuming an intra-cluster correlation of 0.015 and an attrition rate of 20%, we calculate that a sample size of 240 individuals (120 per arm, 50 clusters per arm) is required to detect superiority with a type I error of 0.05 and a statistical power of 80%.

Study Duration and Schedule	The follow-up period for the TwiC is twelve months for the evaluation of the primary endpoint. We plan to enrol first participants in March 2023 and expect an enrolment period of around four months. To assess the sustained effect of the intervention, the overall follow-up period will last 48 months. Thus, the primary endpoint assessment for the last participants is planned end of 2027.
Study Centre(s)	Scientific project lead: Division of Clinical Epidemiology, University of Basel Implementation lead: SolidarMed Lesotho Study sites: 100 (90 to 112) villages in rural areas of Butha-Buthe and Mokhothlong districts in Lesotho
Statistical Analysis	Analyses will be performed following the principles for analysis of cluster-randomized trials in health research as first enunciated by Donner and Klar[20]. Villages are our unit of random selection and individuals the unit of analysis. The primary analysis will be the comparison of mean HbA1c between the two study arms. Superiority will be assessed in an intention-to-treat (ITT) set, i.e. as randomized, using linear mixed-effect regression models, adjusted for clustering and stratification variables as well as baseline fasting blood glucose, irrespective of the uptake of and adherence to the intervention, excluding participants that died, became pregnant, confirmed to move out from the village, or withdrew consent. Baseline characteristics will be described by study arm with summary statistics such as median and interquartile range or number and percentage. Secondary endpoints will be reported using descriptive statistics such as mean and 95% Wald confidence intervals, frequency and percentages. Further details will be outlined in the statistical analysis plan (SAP).
Ethical consideration	This project will be carried out in accordance with the research plan outlined in this protocol and with principles enunciated in the current version of the Declaration of Helsinki as well as all national legal requirements and guidelines as applicable. This protocol will be reviewed by the Ethikkommission Nordwest- und Zentralschweiz (EKNZ, Ethics Committee of Northern and Central Switzerland) and by the National Health Research Ethics Committee (NHREC) of Lesotho before starting the study. Participation in the ComBaCaL cohort study and the TwiC intervention are voluntary. Potential risks associated with study participation include inadequate management by lay CC-VHWs. We will minimize this risk by providing adequate training, continuous supervision by health care professionals, and close guidance through the ComBaCaL eHealth application. Community-based care delivery is widely implemented in HIV care in Lesotho providing substantial benefits compared to purely clinic-based care. The here-presented intervention has the potential to increase the quality of care for T2D by improving access to treatment, increasing adherence and providing closer monitoring. The evidence generated in this study aims at informing future national and international clinical guidelines to improve chronic disease care in low-resource settings. Additionally, the community-based activities of the ComBaCaL project provide the added benefit of building a healthy and friendly community environment through community advocacy and participation, and helping to raise awareness and knowledge of chronic diseases within villages in Lesotho. Thus, the intervention is likely to have a direct positive impact on health outcomes of participants as well as generating evidence to improve context-specific NCD care delivery on a longer perspective.

3 BACKGROUND INFORMATION

3.1 Burden of type 2 diabetes

Globally, 9.3% of the adult population or 436 million individuals were estimated to be living with diabetes in 2019. Until 2045 this number is expected to increase by more than 50% to over 700 million.[1,2] Four out of five people affected by diabetes are currently living in low- and middle-income countries (LMICs). The proportional burden of LMICs continues to rise as most of the projected global prevalence increase over the next decades is expected to occur in LMICs.[3]

Over 90% of all diabetes cases are due to type 2 diabetes (T2D) which is also the main driver of the projected increase in overall diabetes cases[1]. The increase in T2D prevalence is caused by ageing populations and changing lifestyles with decreasing levels of physical activity and higher caloric diets and associated obesity.[4]

Currently, only half of the people living with diabetes are aware of their high blood sugar levels and the associated health risks.[1,2] The risk for diabetes to remain undetected and untreated and therefore lead to earlier complications is significantly higher in LMICs than in high-income countries.[3,5] At the same time, the management of diabetes complications is costly and not accessible in most LMICs in sub-Saharan Africa and elsewhere, therefore prevention via risk factor control and adequate antidiabetic treatment before onset of complications is essential.[6,7] Setting-specific, affordable and scalable solutions need to be developed as it is not possible to directly reproduce strategies from high-income countries in resource-scarce settings[7].

Lesotho is a landlocked country within South Africa, a typical example of an African LMIC where NCDs are overtaking HIV and other infectious diseases as major cause of disability, morbidity and early death[21]. A recent population-based survey in the districts of Mokhotlong and Butha-Buthe has revealed an T2D prevalence of 4% in the adult population in urban and rural areas combined and a relatively high treatment control rate of 40% compared to other LMICs (NH-REC 130-2021).

3.2 Decentralized healthcare delivery

Effective, affordable, scalable setting-specific strategies are required to reverse the trend of increasing NCD-related burden in LMICs. The task-shifting to lay healthcare workers (LHWs) at community-level has been identified as a promising and cost-effective solution to increase access to T2D treatment in LMIC-settings[7,9,12,13,22,23]. Many LMICs have established LHW systems that may be capacitated to play a more active role in the management of NCDs[10,24]. Traditionally, most LHW systems focus on maternal and neonatal health and communicable diseases, especially HIV/AIDS[25–27], however in recent years, increasing evidence has emerged showing a beneficial effect and high cost-effectiveness of LHW-based models on diseases outside this traditional scope, especially for NCDs, such as T2D or arterial hypertension (aHT)[9,10,12]. For T2D, most studies about LHW-led care models have focused on screening, counselling, educational, self-management and referral interventions, while knowledge about the effect of LHW-led prescription of antidiabetic medication is lacking.[7–9,11–13,22,28]

Current knowledge gaps include the question of whether prescription of first-line antidiabetics (metformin) and first-line lipid-lowering treatment (statin) can be included safely and effectively in LHW-led T2D care models at community-level complementing the screening, counselling and referral services for which benefit has been shown already.

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

been adopted many years ago[29]. Despite a drastic health workers shortage in Lesotho (0.9 doctors and 10.2 nurses per 10,000 inhabitants, particularly in the rural areas where the majority of the population lives (77.6%)[30], and the second-highest adult HIV prevalence globally (21.1%)[31], Lesotho has managed to reduce HIV transmission and AIDS-related deaths considerably. This success is based on decentralized HIV testing and care, involving lower cadre healthcare workers and lay VHWs to deliver accessible and equitable services for the urban and rural population alike. Currently the community-based health care delivery in Lesotho is focused on HIV, maternal and neonatal diseases, largely neglecting NCDs. Thus, NCD screening, diagnosis, management and prevention are located at the health facilities. However, due to high workload, staff shortages, lack of specific training, medication stock-outs and outdated guidelines, NCD services are often not delivered adequately at facility-level.

The Ministry of Health (MoH) of Lesotho has proposed in its NCD strategic plan that lessons learnt from HIV program should be incorporated into the NCD care and that delivery platforms should provide integrated HIV/NCD services.[32] Although various modelling studies from the region suggest that integrated service delivery can be cost-effective, robust evidence around community HIV/NCD delivery platforms and their key enablers is missing.[27,33] To our knowledge, no studies have been conducted or policy documents developed on how to provide pragmatic and scalable prevention and treatment models for T2D or other NCDs in the context of a high communicable disease burden in Lesotho.

With the ComBaCaL project, we plan to tackle the growing NCD pandemic through a multi-disciplinary research and implementation partnership. ComBaCaL aims at establishing and validating a community-based care model focused on ehealth supported NCD service delivery by lay CC-VHWss. The ComBaCaL cohort study provides the platform for the scientific assessment of the community-based NCD care model proposed.

In the here described trial within the cohort (TwiC), we are aiming to assess the effect of a community-based T2D care package which includes provision of first-line antidiabetic (metformin) and lipid-lowering (statin) treatment for uncomplicated T2D and treatment support for complicated T2D provided by lay CC-VHWs. The TwiC intervention has been developed based on a local NCD prevalence survey and burden assessment (NH-REC 130-2021), a scoping literature review[14], multiple workshops with different stakeholders in Lesotho and the ComBaCaL pilot cohort study (NH-REC 176-2021). In the intervention clusters, CC-VHWs operating within the existing healthcare system will be capacitated to screen for and diagnose T2D, to prescribe and monitor first-line antidiabetic and lipid-lowering treatment for uncomplicated T2D and to offer treatment support for complicated T2D supported by a tailored clinical decision support application (ComBaCaL app) in their villages. The control group consists of people diagnosed with T2D living in villages that are also part of the ComBaCaL cohort but not sampled for the intervention (control villages), where CC-VHWs will only screen for and diagnose T2D with subsequent standardized counselling and referral to the closest health facility if T2D is present, but no village-based prescriptions.

4 OBJECTIVES AND PURPOSE

4.1 Objectives

The overall objective of the ComBaCaL cohort study and nested TwiCs is to assess the impact of eHealth-supported, lay-led chronic disease control measures in rural Lesotho.
In this T2D TwiC, we will assess the effect, safety and feasibility of a community-based T2D care package which includes the offer of first-line oral antidiabetic and lipid-lowering treatment for uncomplicated T2D by lay CC-VHWs in comparison to facility-based care after community-based screening and diagnosis.

4.1.1 Primary objective

- To assess the effect of community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho on blood sugar control among non-pregnant adults with uncomplicated, uncontrolled (fasting blood glucose (FBG) ≥ 7mmol/l) T2D

4.1.2 Secondary objectives

- To assess the effect of community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho on blood sugar control among non-pregnant adults with uncomplicated, uncontrolled T2D and a baseline HbA1C of ≥6.5%
- To assess the effect of community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho on blood sugar control among non-pregnant adults with T2D and a baseline HbA1C of ≥6.5% independent of complicated or uncomplicated T2D
- To assess the effect of community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho on blood sugar control among non-pregnant adults with T2D independent of baseline HbA1C and FBG values and independent of complicated or uncomplicated T2D
- To assess the sustained safety and feasibility of CC-VHW led, eHealth supported T2D care and sustained effect on reaching blood sugar control, 10-year CVD risk, CVD risk factors, linkage to care, engagement in care and adherence to treatment among adults with uncomplicated, uncontrolled T2D and a baseline HbA1C of ≥6.5%

All following secondary and exploratory objectives will also be investigated in the different analysis populations as above.

- To assess the effect of CC-VHW led, eHealth supported T2D care on 10-year CVD risk using the WHO CVD risk prediction tool[15]
- To assess the effect of CC-VHW led, eHealth supported T2D care on CVD risk factors including body-mass index (BMI), abdominal circumference, blood lipid status, tobacco use, physical activity and dietary habits
- To assess the safety of CC-VHW led, eHealth supported T2D care
- To assess the effect of CC-VHW led, eHealth supported T2D care on linkage and engagement in care and on adherence to treatment
- To assess the sustained safety and feasibility of CC-VHW led, eHealth supported T2D care and sustained effect on reaching blood sugar control, 10-year CVD risk, CVD risk factors, linkage to care, engagement in care and adherence to treatment

4.1.3 Exploratory and implementation objectives

- To assess the effect of CC-CHW led T2D care on the number of eligible participants accessing lipid-lowering treatment
- To assess and describe implementation parameters, i.e. acceptance, uptake of and satisfaction with CC-VHW led T2D care among involved stakeholders
- To estimate the costs of CC-VHW led T2D care

- To assess quality indicators of the services provided and the data collected by CC-VHWs, such as completeness of the data collected and adherence to clinical algorithms provided via the eHealth application
- To assess the 10-year CVD risk using the Framingham Risk Score [34] and the Globorisk Score[35,36]
- To assess the effect of CC-VHW led, eHealth supported T2D care on quality of life using the EQ-5D-5L instrument[37], on health beliefs using the Beliefs about Medicines Questionnaire (BMQ) adapted for people living with T2D[38,39] and on diabetes distress using the five item version of the "Problem Areas in Diabetes" (PAID-5) scale [40,41]
- To assess the effect of CCH-VHW led T2D care on self-reported access to care

4.2 Scientific justification of study population

The ComBaCaL cohort study will be located in rural villages of Butha-Buthe and Mokhothlong districts in Lesotho. Lesotho is a typical example of an African LMIC where a developing health system is facing the heavy double-burden of the still highly prevalent infectious diseases HIV/AIDS and TB in combination with a rapidly spreading NCD epidemic[21].

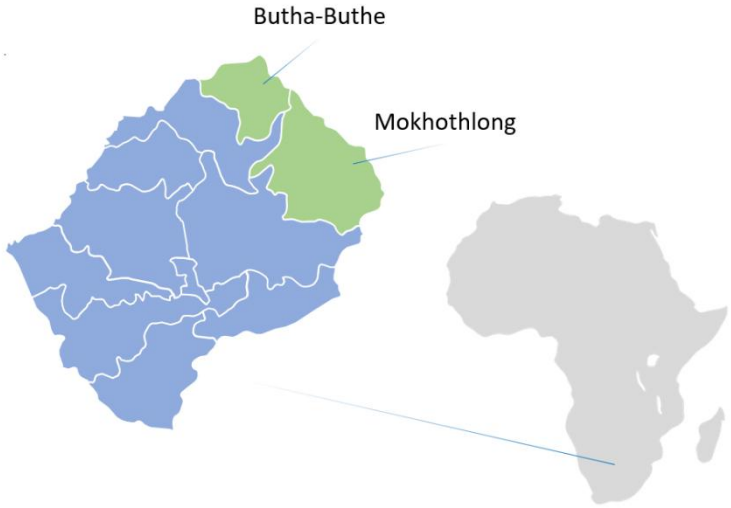

Figure 1 Map of Lesotho with the two districts Butha-Buthe and Mokhothlong

In the Lesotho health system, the VHW program plays a crucial role and has proven highly effective for the control of HIV/AIDS, especially for remote rural areas[29]. The Lesotho VHW program thus represents a meaningful starting point for implementation research on enhancing community-based intervention strategies and provides a setting that is representative for the health systems in many other LMICs, especially in sub-Saharan Africa, where lay worker led care has a similar standing.

5 STUDY DESIGN

5.1 Primary hypothesis, primary estimand and analysis sets

Primary hypothesis: Community-based, CC-VHW-led, eHealth supported T2D care in rural Lesotho is safe and superior with regard to HbA1c levels twelve months after enrolment compared to facility-based T2D care among non-pregnant adults with uncomplicated uncontrolled T2D.
Primary estimand: HbA1c reduction (mean difference) 12 months after enrolment between community-based, CC-VHW-led, eHealth supported T2D care versus facility-based T2D care, in non-pregnant adults with uncomplicated uncontrolled T2D who were still alive and did not move out of their village, irrespective of the uptake of the intervention, T2D treatment, T2D treatment adherence and adverse events.
Primary analysis set: All study participants with uncomplicated, uncontrolled T2D at baseline, defined as:

- Uncomplicated: No or only Metformin treatment
- Not meeting criteria for direct referral, which are defined as:
  - FBG > 14 mmol/l OR
  - RBG > 16.7 mmol/l OR
  - Having polyuria, polydipsia and weight loss
- Uncontrolled: FBG ≥7 mmol/l

Secondary analyses sets:

a) Only study participants with uncomplicated and uncontrolled diabetes and a baseline HbA1c ≥ 6.5%
b) Only study participants with a baseline HbA1c ≥ 6.5%
c) All study participants

5.2 Endpoints

For the endpoint assessments at twelve months, a range of 300 to 420 days after enrolment applies. For the endpoint assessments at six months, a range of 150 to 210 days applies. For endpoint assessments after twelve months, endpoint windows of 180 days apply.
The primary and secondary endpoints will first be assessed in the primary analysis set, following the primary hypothesis and primary estimand. Secondly, the primary and secondary endpoints will be assessed in the secondary analysis sets. The analyses in the secondary analysis set that includes all study participants will explore the effects of our intervention among the entire non-pregnant T2D population including those with more intensive treatment.

5.2.1 Primary endpoint

- Mean HbA1c twelve months after enrolment

5.2.2 Secondary endpoints

- 10-year risk for a fatal or non-fatal CVD event estimated using the WHO CVD risk prediction tool[15,16] at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Mean HbA1c at six months after enrolment, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Mean FBG at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Proportion of participants with an HbA1c < 8% at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Proportion of participants with an FBG < 7 mmol/l at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 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)[42] adapted to the local context and language according to the IPAQ recommendations[43], dietary habits using a shortened unquantified food frequency questionnaire adapted from an assessment tool for

obesity used in South Africa[44] and alcohol and tobacco use at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment

- Linkage to care: proportion of participants not taking treatment at enrolment who have initiated pharmacological antidiabetic treatment at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 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 (CC-VHW or healthcare professional) within the two weeks prior to assessment at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 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, as well as within subsequent time intervals during a total follow-up period of up to 48 months after enrolment
- Self-reported adherence to treatment at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment

5.2.3 Exploratory endpoints and implementation indicators

- Number of consultations at a health facility and with the CC-VHW within six and twelve months, as well as within subsequent time intervals during a total follow-up period of up to 48 months after diagnosis
- 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 T2D 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, as well as within subsequent time intervals during a total follow-up period of up to 48 months after enrolment
- Proportion of participants who are reaching treatment targets (FBG <7 mmol/l) and are reporting no intake of antidiabetic medication in the two weeks prior to assessment at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Proportion of participants accessing lipid-lowering medication at six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Participants', CC-VHWs' and involved health care professionals' perception of the risks, benefits and problems of community-based management of uncomplicated T2D by CC-VHWs
- Quality indicators of the CC-VHW activities, such as completeness of the data collected and adherence to clinical algorithms provided via the eHealth application
- Causes for the stop or interruption of treatment or switch to health facility-based treatment after initiation by CC-VHWs in the community
- Health system costs and individual costs for participants for the management of their condition within the first six and twelve months, as well as within subsequent time intervals during a total follow-up period of up to 48 months follow-up period of up to 48 months after enrolment after diagnosis
- 10-year CVD risk estimated using the Globorisk score[36] and Framingham Risk Score [34] six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Quality of life using the EQ-5D-5L instrument[37], health beliefs using the Beliefs about Medicines Questionnaire (BMQ) adapted for people living with T2D[38,39] and diabetes distress using the five item version of the "Problem Areas in Diabetes" (PAID-5) scale[40,41] after twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment
- Self-reported access to care and access to medication

- Type and dosage of antidiabetic and lipid-lowering medications prescribed by CC-VHWs or healthcare professionals six and twelve months, as well as at subsequent timepoints over a total follow-up period of up to 48 months after enrolment

5.3 Randomization

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

5.4 Measures to minimize bias

5.4.1 Blinding

Participants are not blinded to the intervention due to the nature of the intervention. However, due to the cluster level randomization and TwiCs approach participants are blinded to the allocation (i.e. participants in the control villages are not aware of the intervention being implemented in the intervention villages).
The CC-VHWs who are enrolling participants, providing the intervention and collecting the date cannot be blinded to the intervention nor the allocation. However, the main outcome is a laboratory measurement and the safety endpoints are assessed by an independent study physician blinded to the allocation.
The statistician and data managers cannot be blinded to the allocation.

5.4.2 Measurements

Baseline and endpoint assessments will be conducted by CC-VHWs supported by the ComBaCaL app. If resources allow, certain endpoints (i.e. HbA1c) will be assessed by study staff not involved in the care delivery at village level. Protocols and instructions for correct measurements and sample collection as well as structured questionnaires for the assessment of lifestyle risk factors, health beliefs, diabetes distress and quality of life are provided in the ComBaCaL app. For the duration of the study there will be regular field visits by supervising CC nurses to ensure that procedures for data collection are correctly followed by all involved CC-VHWs.

5.5 Study duration and duration of participant's participation

The follow-up period for this TwiC is twelve months for the evaluation of the primary endpoint. We plan to enrol first participants in March 2023 and expect an enrolment period of around four months. To assess the sustained safety and effect of the intervention, the overall follow-up period will last for 48 months. Thus, the endpoint assessment for the last participants is planned for end of 2027.

5.6 Amendments

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

5.7 Withdrawal and discontinuation

5.7.1 Individual level

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

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

5.7.2 Study and cluster level

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

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

The Principal Investigator in consultation with Co-Investigators may choose to pause or discontinue the ComBaCaL cohort study in certain or all villages or to pause or discontinue the intervention in one or more intervention villages.
We refer to the "ComBaCaL cohort study protocol" for details regarding the criteria for interruption or stop of the ComBaCaL cohort study. If the ComBaCaL cohort is being interrupted or stopped in one or more villages, automatically also the nested TwiCs are interrupted or stopped in the concerned villages, while the participants will remain in the TwiC analysis population as outlined in section 9.

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

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

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

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

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

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

5.8 End of trial

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

6 SELECTION OF STUDY PARTICIPANTS

6.1 Selection of villages

We refer to the "ComBaCaL cohort study protocol" for detailed information about the selection of villages for the ComBaCaL cohort.
Out of the ComBaCaL cohort villages, 50% will be randomly allocated to the intervention group. We refer to the paragraph **Error! Reference source not found.** "Randomization" for information about the random allocation.

6.2 Recruitment of participants

We refer to the "ComBaCaL cohort study protocol" for details regarding the recruitment for the ComBaCaL cohort. For this TwiC, CC-VHWs will screen for eligible individuals among adult ComBaCaL cohort participants in their villages via home visits according to the following criteria.

6.2.1 Inclusion criteria

- Participant of the ComBaCaL cohort study (signed informed consent available)
- Aged 18 years or above
- Living with T2D, defined as reporting intake of antidiabetic medication or being newly diagnosed during screening via standard diagnostic algorithm (see appendix of the "ComBaCaL cohort study protocol")

6.2.2 Exclusion criteria

- Known type 1 diabetes mellitus
- Reported pregnancy

Participants in the intervention villages will be offered the intervention T2D care package including first-line antidiabetic treatment (metformin) for eligible participants, lifestyle counselling and lipid-lowering medication (statin) by the CC-VHW after the screening. Participants are free to accept or reject all or parts of the pharmacological and non-pharmacological treatment offered by the CC-VHW.
Data of ComBaCaL cohort participants living in villages not selected for the intervention will be used as control arm. As per the ComBaCaL cohort study protocol and informed consent, no specific recruitment or participant information will be provided to the participants in control villages.

7 STUDY PROCEDURES

7.1 General Setting

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

7.2 Screening

Screening and diagnosis for T2D among the ComBaCaL cohort members will be conducted by CC-VHWs according to the algorithms provided in the appendix of the "ComBaCaL cohort study protocol". These algorithms are being encoded into the ComBaCaL app, guiding the question logic for data collection and serving as clinical decision aid for the CC-VHWs. After diagnosis of T2D, CC-VHWs will screen for the other eligibility criteria and based on the screening information, the trial eligibility will be determined via the ComBaCaL app.

7.3 Enrolment

ComBaCaL cohort participants meeting the eligibility criteria for the TwiC, will automatically be included in the TwiC population. We refer to the current version of the "ComBaCaL cohort study protocol" and to the section 12.3 of this document for details regarding the consent procedures. Participants in intervention villages may reject the intervention at any time during the study and request referral to a health facility for the continuation of their treatment. Participants consenting to participation but subsequently rejecting care offered by the CC-VHW might be approached for qualitative inquiry on the reasons for the refusal of community-based care.

7.4 Baseline

Most baseline data to describe the TwiC participants will be collected as part of the ComBaCaL cohort assessments (see current version of the "ComBaCaL cohort study protocol" for details). In brief, the following data will be collected by the CC-VHW at cohort baseline using the ComBaCaL eHealth application: age, sex, height, weight, abdominal circumference, household position, socioeconomic indicators of the household, level of education, income-generating activity, targeted medical history including previous T2D diagnosis, intake of antidiabetic medication, HIV status and cardiovascular complications, physical activity using the validated International Physical Activity Questionnaire Short Form (IPAQ-SF)[42] adapted to the local context and language according to the IPAQ recommendations[43], dietary habits using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa[44], self-reported alcohol and tobacco use. Participants will also be screened for aHT.

In addition to the data collected as part of regular ComBaCaL cohort activities, further baseline information will be collected for TwiC participants based on the International Consortium for Health Outcomes Measurements' (ICHOM) data collection reference guide for sets for diabetes in adults[45]. Data collected at TwiC baseline include HbA1c, blood lipids, quality of life using the EQ-5D-5L instrument[37], health beliefs using the Beliefs about Medicines Questionnaire (BMQ) adapted for people living with T2D[38,39], self-reported access to care and diabetes distress using the five item version of the "Problem Areas in Diabetes" (PAID-5) scale[40,41].

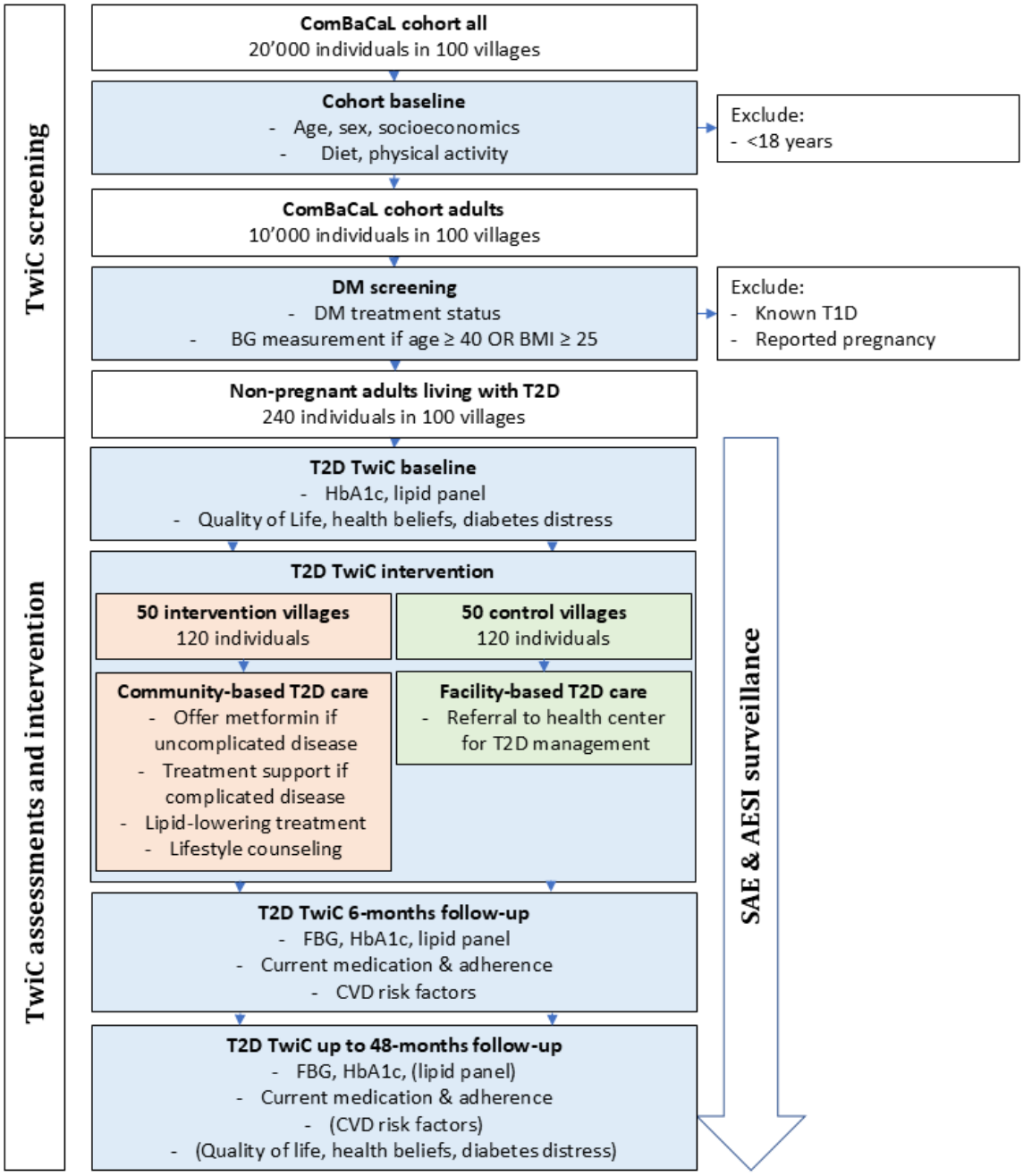

Figure 2 Flow of events. FBG: Fasting Blood Glucose, CVD: Cardiovascular Disease, SAE: Serious Adverse Event, AESI: Adverse Event of Special Interest, T2D: Type 2 Diabetes, T1D: Type 1 Diabetes

7.5 Intervention

In the intervention villages, CC-VHWs will offer a T2D care package including lifestyle counselling, first-line antidiabetic (metformin) and lipid-lowering (statin) treatment for uncomplicated T2D and treatment support and regular check-ups for complicated T2D at village-level according to clinical algorithms based on international guidelines for primary healthcare management of T2D[46,47] and the updated Lesotho Standard Treatment Guidelines (under review at the time of writing this protocol).

Where feasible, CC-VHWs might also provide refill services for other chronic medication upon prescription of a nurse or doctor at the health center in charge. Patients with history of a cardiovascular event will be offered antiplatelet treatment (aspirin) in line with local guidelines.
The CC-VHWs in the intervention villages will receive specific training focused on lifestyle counselling, drug prescription, screening for potential adverse events of drugs administered, and disease monitoring and dose adjustment after treatment initiation.
Direct guidance for treatment initiation, drug prescription, counselling and monitoring will be provided via the ComBaCaL app. All activities conducted by CC-VHWs in the communities, including counselling and drug prescription, will be captured in the same application.
Health care professionals and supervising study staff will monitor all activities in a web version of the app and will be intervening in case of missing data, non-adherence to the clinical algorithms, or unclear clinical conditions. The CC-VHWs may always request support by supervising health care professionals.
In case of complicated disease (i.e. if treatment targets are not reached with metformin alone), unclear diagnosis, relevant comorbidities or presence of clinical alarm signs or symptoms, participants will be referred to the closest health facility for further management. Participants are free to accept or refuse the treatment offered by the CC-VHWs. Participants refusing the CC-CHW-led treatment will be asked about the reasons for the refusal and will be referred to the responsible health facility for further management.
In control villages, CC-VHWs will refer participants to the responsible health facility for therapeutic management after enrolment and baseline assessment.

7.6 Follow-up and endpoint assessment

7.6.1 Scheduled follow-up visits and endpoint assessments

Follow-up visits by CC-VHWs including endpoint assessments will be scheduled six months (range 150 to 240 days) and twelve months (300 to 420 days), 18 months (450 to 630 days), 24 months (630 to 810 days), 30 months (810 to 990 days), 36 months (990 to 1170 days), 42 months (1170 to 1350 days), and 48 months (1350 to 1530 days) after TwiC enrolment. If resources allow, certain endpoints (i.e. HbA1c) will be assessed by study staff not involved in the care delivery at village level.
During the follow-up visits, HbA1c measurements will be conducted together with the collection of secondary endpoint data such as blood glucose, CVDRFs (physical activity, diet, blood lipid status, tobacco and alcohol use using the same assessment tools as for the baseline, height, weight, BMI, abdominal circumference), engagement in and adherence to antidiabetic treatment, quality of life, health beliefs and diabetes distress.
All mentioned endpoints will be collected at six and 12 months. For follow-up visits beyond 12 months not all endpoints will be collected at every visit to avoid overburdening of the CC-VHWs and the participants. Specifically, physical activity, diet, blood lipid status, quality of life and health beliefs will only be assessed if deemed feasible and relevant.
During follow-up visits, CC-VHWs will inquire about relevant clinical events since the previous visit (including screening of the Bukana for documentation of respective events). These events will be documented in a dedicated electronic case report form within the ComBaCaL app. Safety outcomes of this TwiC (SAEs and AESIs, see section 8 for definitions) are a subset of the clinically relevant events that are captured as part of the ComBaCaL cohort study. Reports of SAEs and possible AESIs will be reviewed by the study physician for final assessment and classification.
In addition, specific questionnaires about participants' satisfaction and acceptability of the TwiC intervention will be administered and semi structured interviews conducted with a selection of participants, CC-VHWs and involved health care professionals will be conducted to qualitatively explore perceived risks, benefits and problems of community-based therapeutic management of uncomplicated T2D. We will evaluate the quality of services provided and the data collected in the villages by analysing aggregated data and metadata of the reports submitted by the CC-VHWs via the eHealth application.

7.6.2 Clinical follow-up

In intervention villages, the CC-VHWs will conduct clinical follow-up visits according to the clinical algorithms provided in the appendix. During these clinical follow-up visits, CC-VHWs will check BG values,

monitor treatment adherence, check for treatment side effects, adjust treatment dose if required, provide lifestyle counselling and refer participants to the responsible health facility, if treatment targets are not met under metformin alone or in case of side effects, clinical alarms signs or symptoms or relevant comorbidities. The therapeutic management provided by the CC-VHWs under guidance of the ComBaCaL app is in line with international guidelines on the treatment of T2D at primary healthcare level[46,47] and the then valid Lesotho Standard Treatment Guidelines.

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

7.7 Schedule of events

	Cohort baseline	TwiC screening & baseline	Intervention follow-ups[1]	6-month follow-up	12-month follow-up	Beyond 12-months and up to 48 months follow-up
Time in days relative to TwiC enrolment	**-60 – 0**	**0**	**0 – 420**	**150 – 240**	**300 – 420**	**450-1530**
ComBaCaL cohort informed consent	x					
Date of birth	x					
Height, weight, abdominal circumference	x			x	x	X
Sociodemographics	x					
Short medical history[2]	x					
CVDRFs[3]	x			x	x	(x)[10]
FBG	x			x	x	X
HbA1c		x		x	x	x
Diabetes distress[4]		x	x	x	x	(x)[10]
Health beliefs[5]		x			x	(x)[10]
Quality of life[6]		x		x	x	(x)[10]
Blood lipid status (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides)		x		x	x	(x)[10]
Adherence to antidiabetic medication		x	x	x	x	X
Acceptability & satisfaction with T2D care[7]				x	x	(x)[10]
Screening for relevant clinical events	x	x	x	x	x	X
Screening for clinical alarm signs/symptoms	x	x	x	x	x	X
TwiC Control						
Referral to health facility[8]		x		x	x	x
TwiC Intervention						X
Offer metformin		x	x	x	x	x
Offer lipid-lowering treatment		x	x	x	x	x
Provide lifestyle counselling		x	x	x	x	x
Referral to health facility[9]		(x)	(x)	(x)	(x)	(x)

1) Only for TwiC participants in intervention villages
2) Including personal and family history for T2D / DM and other relevant conditions
3) Physical activity using IPAQ-SF[42], dietary habits[44], tobacco and alcohol use
4) Using the 5-item Problem Areas in Diabetes (PAID-5) scale[41]
5) Using the Beliefs about Medicines Questionnaire[38,39]
6) Using the EQ-5D-5L instrument[37]
7) Only for a subset of participants
8) For initiation or continuation of T2D treatment and/or in case of clinical alarm signs or symptoms
9) In case of clinical alarm signs or symptoms, participants refusing community-based T2D care, complicated disease, unclear diagnosis or relevant comorbidity
10) Assessment will not be taken every 6 months after primary 12 months study follow-up. Frequency will depend on VHW workload and considerations on scientific value of reassessments.

8 SAFETY CONSIDERATIONS

8.1 Definition and documentation of safety outcomes

Adverse event (AE)	Any untoward medical occurrence in a study participant, including occurrences that are not necessarily caused by or related to the study procedures
Adverse event of special interest (AESI)	AE consistent with complication of T2D, such as: • Myocardial infarction • Stroke • Symptomatic heart failure • Chronic kidney disease • Blindness, severe vision impairment AE probably related to intake of antidiabetic medication, such as: • Intolerance reaction against antidiabetic medication leading to discontinuation of the medication concerned (including allergic reactions, drug interactions or rare severe side effects)
Serious adverse event (SAE)	Any AE that: • Results in death • Is life-threatening • Requires hospitalization or prolongation of existing hospitalization ○ Hospitalizations due to uncomplicated delivery are not considered as SAE • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect
Serious adverse event of special interest (SAESI)	SAE consistent with complication of T2D, such as: • Myocardial infarction • Stroke • Symptomatic heart failure • Chronic kidney disease • Blindness, severe vision impairment SAE probably related to intake of antidiabetic or antidiabetic medication, such as: • Intolerance reaction against antidiabetic medication leading to discontinuation of the medication concerned (including allergic reactions, drug interactions or rare severe side effects)

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

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

- Active reporting by participants or friends or relatives outside of scheduled CC-VHW visits (scheduled visits are defined as visits being triggered through the ComBaCaL app based on regular or clinical follow-up algorithms or visits being assigned by supervising healthcare professionals)
- Passive reporting by participants or friends or relatives after inquiry by CC-VHWs during scheduled VHW visits
- Clinical observation of CC-VHWs during or outside scheduled CC-VHW visit
- Screening of participants' Bukanas (personal health booklet)
- Reporting by health centre nurses

In intervention villages, additional visits are scheduled for the therapeutic management of T2D during which CC-VHWs will conduct additional AE screening including specific screening for AEs possibly related to the therapeutic intervention. The intervention-specific AE screening will be closely guided via the eHealth application (i.e. a list of symptoms to be inquired for each drug will be provided).

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

8.2 Causality of SAEs and AESIs

A causality assessment of all SAEs and of AESIs possibly related to the therapeutic management of T2D will be performed by the study physician based on the reports submitted by the CC-VHWs. As a result of the causality assessment, the study physician will provide a statement whether the SAE/AESI is possibly, likely or definitely related or unrelated to the T2D care provided.

8.3 Management of AEs

8.3.1 Control villages

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

8.3.2 Intervention villages

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

8.4 Reporting

CC-VHWs will document SAEs and AESIs in dedicated electronic case report forms (eCRFs) in the ComBaCaL app with subsequent assessment and classification by the study physician. All deaths and all other SAEs that are possibly, probably or definitely related to the study intervention, will be reported to the principal investigator within one month after the study physician has become aware of the event.
All deaths and all other SAEs that are possibly, probably or definitely related to the study intervention will be reported to the NH-REC on a yearly basis.

9 STATISTICS

9.1 Determination of sample size

The ComBaCaL cohort will consist of inhabitants of around 100 (range 90-112) randomly selected villages in rural Lesotho. The estimated mean number of adult ComBaCaL participants per village is 100 resulting in an estimated 10'000 adult cohort participants. Sample size for this TwiC is calculated assuming an individual randomization inflated by a design effect that account for variation at cluster level, according to the code developed by Rotondi and Donner[19]. Based on preliminary results from an NCD prevalence survey in the region (NH-REC ID 139-2021), we expect the prevalence of T2D in the adult population in the rural setting in Lesotho to be around 4%, with about 60% of people living with T2D fulfilling the criteria for the primary analysis set (not pregnant, no type 1 diabetes mellitus, uncomplicated and uncontrolled T2D). Hence, considering an average cluster size of 100 adult inhabitants, the mean number of inhabitants eligible for the TwiC is 2.4 per village. We estimate an effect size of 0.6% HbA1c mean difference between the two groups after 12 months. Assuming an intra-cluster correlation of 0.015 and an attrition rate of 20%, we calculate that a sample size of 240 individuals (120 per arm, 50 clusters per arm) is required to detect superiority with a type I error of 0.05 and a statistical power of 80%.

9.2 Description of statistical methods

Analyses will be performed following the principles for analysis of cluster-randomized trials in health research as outlined by Donner and Klar[20].
All analyses will be done using Stata[48] or R[49].

9.2.1 Datasets to be analysed

All analyses sets are defined above (Chapter 5.1).
All analyses sets will be analyzed according to an intention-to-treat ITT analysis, i.e., all participants analyzed as randomized.

9.2.2 Primary analysis

Primary endpoint assessment will be done in the ITT set as defined above.
We will use a linear mixed-effect effect regression model with random intercept at the level of the clusters to assess the effect of the intervention, while accounting for variability across the clusters and after adjusting for potential socio-demographic confounders.
Superiority will be assessed according to regression coefficient and statistical significance will be based in 2-sided tests at the alpha level of 0.05.
No per protocol or as-treated analyses are planned since they are vulnerable to bias. However, we are considering a Complier Average Causal Effect (CACE) analysis to assess the impact of compliance with the intervention as this provides a more unbiased treatment effect than a per protocol or as-treated analysis and the underlying assumptions for such an instrumental variable approach are given. We will obtain the CACE estimator using a "two-stage least squares" (TSLS) approach, which jointly models the two processes of participation and outcome (i.e. regression model of participation, and regression model predicting the outcome, given participation). Such a TSLS approach yields more accurate estimates and confidence intervals, than simply dividing the mean effect estimate by the proportion of compliers[50].

9.2.3 Secondary analysis

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

9.3 Handling of missing data

Participants with missing covariates will be imputed using multiple imputation chained equation techniques. Further details of missing data will be outlined in the SAP.

10 DESCRIPTION OF DATA MANAGEMENT

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

11 QUALITY CONTROL AND QUALITY ASSURANCE

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

12 ETHICAL CONSIDERATIONS

12.1 Independent Ethics Committees (IECs)

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

12.2 Risk-benefit ratio

There is no substantial health risk associated with participation in this study. The T2D screening, diagnosis and management offered will be conducted in line with national and international recommendations. All participants found to be at risk for a relevant medical condition will be referred to the responsible health facility for professional work-up and care.
Data collection will entail questionnaires and capillary blood measurements for HbA1c, BG and blood lipids. These procedures do not have the potential to cause significant harm to participants.
No personalized data of participants will be shared with people other than the directly involved study team members if not agreed upon by the participant.
The access to guideline-conform active community-based NCD screening will likely increase early case detection and thus improve access to potentially life-saving treatment. Additionally, follow-up in the community by CC-VHWs with re-linking services is likely to improve T2D care for participants.
Potential risks associated with the TwiC intervention include inadequate management by lay CC-VHWs. We will minimize this risk by assuring adequate training, continuous supervision by health care professionals, and close guidance through the ComBaCaL eHealth application. Community-based care delivery is widely implemented in HIV care in Lesotho providing substantial benefits compared to purely clinic-based care.
The evidence generated in this study may inform future national and international clinical guidelines to improve NCD care in low-resource settings. Additionally, the community-based activities provide the added benefit of building a healthy and friendly community environment through community advocacy and participation, and may help to raise awareness and knowledge of NCDs within participating villages. Thus, the ComBaCaL project is likely to have a direct positive impact on health outcomes of participants as well as generating evidence to improve context-specific NCD care on a longer perspective.
This project will be carried out in accordance with the research plan outlined in this protocol and with principles enunciated in the current version of the Declaration of Helsinki as well as all national legal requirements and guidelines as applicable.

12.3 Participant information and consent

The ComBaCaL cohort consent is based on the cmRCT[17] approach, i.e. all cohort participants consent to being randomized as part of a TwiC. Participant information and consent seeking for the ComBaCaL cohort will be conducted by the local ComBaCaL VHW in a three-stepped approach, first orally on village level, secondly orally on household level, and thirdly in written electronic form on individual level. We refer to the “ComBaCaL cohort study protocol” for details.
Participants that are being randomized to the control group, will not be bothered and data collected within the scope of the ComBaCaL cohort will be used for the TwiC analysis without further TwiC-specific information or consent. For villages randomized into the TwiC intervention group, an oral village consent from the village chief will be sought before the intervention will be offered to eligible individuals in the community. Participants may decline any of the offered services without implications on further cohort affiliation and their data will also be used for TwiC analyses. As the intervention does not entail any activities other than the task-shifting of standard-of-care T2D management components from primary healthcare professionals to CC-VHWs, oral intervention consent will be sought as outlined in the “ComBaCaL cohort study protocol”.

Participants will be able to reject care by the CC-VHW in the village at any time during the study and request referral to a health facility. Participants consenting to participation but subsequently rejecting

care offered by the CC-VHW might be approached for qualitative inquiry on the reasons for the refusal of community-based care.

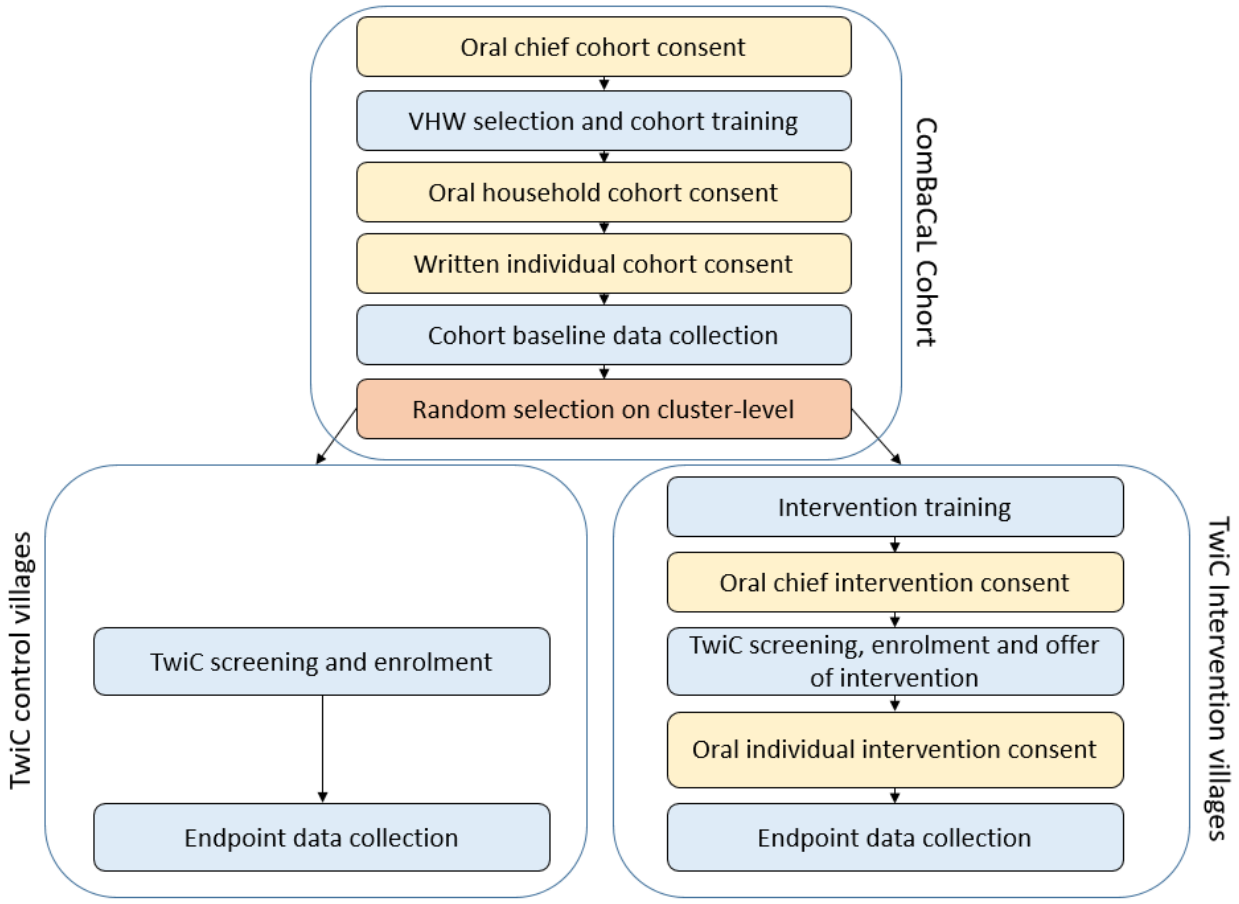

Figure 3 Consent cascade in ComBaCaL cohort and TwiC. Yellow: Consent, Orange: Randomization, Blue: Training or field activity

12.4 Withdrawal on household or individual level

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

12.5 Service delivery for people declining consent

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

12.6 Participant confidentiality

The investigators will ensure that the participants' confidentiality will be maintained at all times during and after the study, following procedures outlined in section 7.3 (enrolment procedures) and section 10 (data management).

12.7 Participants requiring particular protection

Pregnant women with T2D will not be included in the intervention but being referred to the responsible health facility for further assessment and management. The same applies to people with a severe comorbidity with an estimated life-expectancy of less than one year.

This study has a strong service delivery aspect and often people with mental or physical conditions impairing capacity for informed consent are particularly vulnerable to NCDs such as T2D and its

complications. Therefore, we will offer the intervention also to eligible people with impaired judgement if an oral guardian consent for the intervention is provided.

12.8 Participant compensation

No compensation will be paid for participation in the study.

13 FUNDING

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

14 DISSEMINATION OF RESULTS AND PUBLICATION POLICY

14.1 Dissemination to scientific community

International scientific conferences and publications in scientific peer-reviewed journals will serve for wider dissemination of results. Preference will be given to journals with an open-access publication model. Further, anonymised datasets will be made available on open data repositories, such as www.zenondo.org. The study will be registered on ClinicalTrials.gov prior to the start of the trial and a summary of the study protocol will be published in a peer-reviewed journal. The current version of the International Committee of Medical Journal Editors (ICMJE) recommendations is applicable regarding authorship eligibility.[51] The use of professional writers is not intended.

14.2 Information of community and policy makers

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

15 APPENDIX

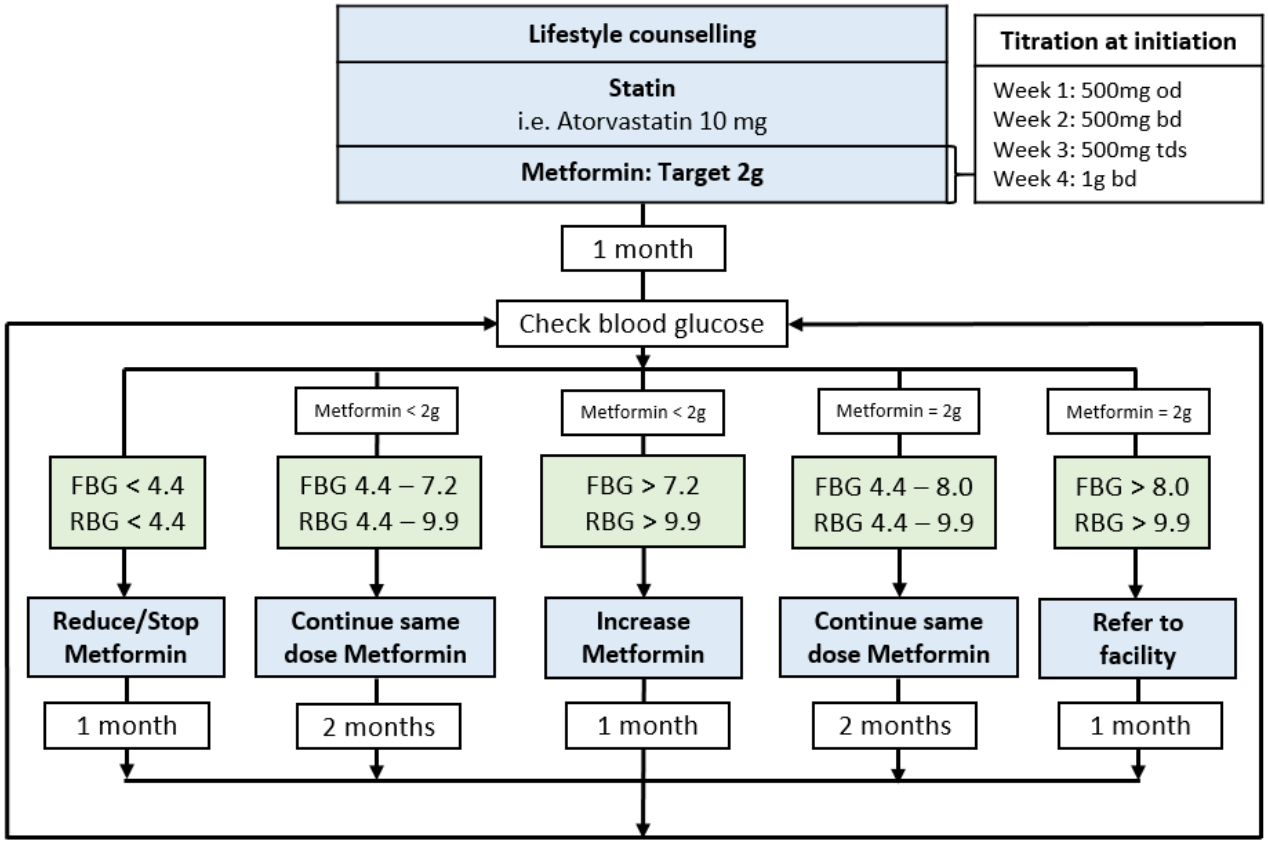

Figure 4 Treatment algorithm for participants with T2D not meeting criteria for direct referral to facility in intervention villages.

Participants with an FBG > 14 mmol/l or a RBG > 16.7 mmol/l or with polyuria, polydipsia and weight loss (independent of blood sugar levels) will be directly referred to a health facility for further check-up and initiation of insulin treatment.
Participants who are receiving complicated treatment defined as either taking insulin or more than one oral antidiabetic will only be offered metformin treatment in the community after recommendation of a healthcare professional (nurse or doctor). The same accounts for participants reporting previous side effects possibly related to any of the treatment components offered.
At every visit, participants will be screened for clinical alarm signs and symptoms as well as for potential complications of T2D. In case of an alarm sign or symptom, the participant will be directly referred to a health facility. The routine staff of the responsible health facility will remain in charge of the clinical care of participants. The CC nurses will be available to provide clinical support if requested by the healthcare staff in charge. For both clinical alarm signs and symptoms and potential complications of T2D, a CC nurse is prompted to follow-up the event and submit a report in the ComBaCaL app.
Before prescribing any drug, participants are screened for potential contraindications, prior side effects to the respective drug and the pregnancy status for female participants under the age of 55 years. In case of possible contraindications, prior side effects to a treatment component or pregnancy, the participant is referred to a health facility for further management.
At every visit, the current medication, possible side effects and treatment adherence will be documented.
As recommended by the local guidelines, aspirin will be offered to participants with a history of stroke or myocardial infarction after evaluating contraindications against the medication. Further, atorvastatin

10mg will be offered to all participants in a fire-and-forget approach after evaluating contraindications against the medication.
CC-VHWs will advise participants to fast at the day of blood sugar check-up. However, if a RBG is available only, treatment adjustments will be conducted according to the above shown algorithm.

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