Study Protocol

Community-Based chronic disease Care in rural Lesotho: The ComBaCaL cohort study

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

Study acronym/ID	ComBaCaL cohort study		
Protocol Version Nr	2.0	Date 22.12.2025	
Project Leaders / Responsible	Prof. Dr. Niklaus Labhardt, MD, DTM&H, MIH Division Head Division of Clinical Epidemiology University Hospital Basel University of Basel Totengaesslein 3, 4001 Basel, Switzerland +4179 870 18 59 niklaus.labhardt@usb.ch		
Funding Agency	Swiss Development Cooperation, World Diabetes Foundation		

1 GENERAL INFORMATION

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

Title	Names	Institution	Position	Function in study
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MSc	Phate-Lesihla Rosina	HIV & AIDS Program, Ministry of Health Lesotho	Clinical Officer	Co-Investigator

MD	Nthuseng Bridgett Marake	HIV & AIDS Program, Ministry of Health Lesotho	HIV Treatment and Care Officer	Co-Investigator
MD	Mamotena Sekhobe	Family Health Division, Ministry of Health Lesotho	Head of Family Health Division	Co-investigator

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

II. Signatures

Study Title: "Community-Based chronic disease Care in rural Lesotho: The ComBaCaL cohort study"

The following project leaders have approved the protocol version 2.0, dated 22.12.2025, 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 Investigators:

- I have read this protocol version 2.0, dated 22.12.2025, 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.

Principal Investigator

Signature		
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Table of contents

III. Abbreviations / Glossary of terms

aHT	Arterial hypertension
ANC	Antenatal care
BMI	Body mass index
BG	Blood glucose
BP	Blood pressure
CC Nurse	Chronic Care Nurse
CESI	Clinical event of special interest
CHT	Community Health Toolkit
cmRCT	Cohort multiple randomized controlled trials
ComBaCaL	Community-Based Chronic Disease Care Lesotho
CVDRF	Cardiovascular disease risk factor
DHMT	District Health Management Team
DKF	Department for Clinical Research
DM	Diabetes mellitus
EKNZ	Ethics Committee of Northern and Central Switzerland
ESC/ESH	European Society of Cardiology/ European Society of Hypertension
FBG	Fasting blood glucose
HbA1c	Glycated haemoglobin

HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IT	Information technology
LMICs	Low- and middle-income countries
MoH	Ministry of Health
MTA	Material transport agreement
MUAC	Mid-upper arm circumference
NCD	Non-communicable disease
NH-REC	National Health Research Ethics Council
PLHIV	People living with HIV
PNC	Postnatal care
PrEP	Pre-exposure prophylaxis
RBG	Random blood glucose
SCE	Serious clinical event
SCESI	Serious clinical event of special interest
SDC	Swiss Agency for Development and Cooperation
SRHR	Sexual and Reproductive Health and Rights
TB	Tuberculosis
TwiC	Trial within cohort
UHC	Universal Health Coverage
UNAIDS	Joint United Nations Programme on HIV/AIDS
VHW	Village health worker
VL	Viral load
WDF	World Diabetes Foundation
WHO	World Health Organization

IV. Synopsis

Project Leaders	Prof. Dr. Niklaus Labhardt
Study Title	Community-Based chronic disease Care in rural Lesotho: The ComBaCaL cohort study
Short Title/Study ID	ComBaCaL cohort study
Protocol Version and Date	Version 2.0, 22.12.2025 The purpose of amended protocol version 2.0 is to expand the scope of the cohort study and to facilitate the preparation for nested trials within cohorts (TwiCs), aimed at generating evidence on integrated community-based prevention and care strategies to support Universal Health Coverage (UHC) in rural Lesotho. In addition to non-communicable diseases (NCDs) and HIV-related conditions, data collection will be broadened to include other conditions and essential health service needs, such as those related to sexual and reproductive health and rights (SRHR) and child health – most of which are traditionally managed by Village Health Workers (VHWs) in Lesotho already. The variables of interest outlined in the original protocol (Version 1.0) mainly remain unchanged, as they were already collected. However, the follow-up period has been extended, and new windows for endpoint collection have been added. The newly included endpoints related to additional health needs and conditions will be monitored from the time of the update onward.
Study Category with Rationale	Cohort study Risk category A
Background and Rationale	Globally, non-communicable diseases (NCDs) are the leading cause of death and disability[1] with a particularly high burden in LMICs, where more than 75% of all premature NCD deaths occur.[2] In Southern Africa, the NCD burden has risen significantly over the past two decades, driven by the increasing prevalence of cardiovascular risk factors such as unhealthy diets, smoking, reduced physical activity, arterial hypertension (aHT), obesity, diabetes mellitus (DM), dyslipidemia, and air pollution.[3–6] At the same time, infectious diseases and health challenges in sexual and reproductive health rights (SRHR) and child health continue to persist – contributing to a situation that presents an increasingly complex burden of diseases requiring novel integrated health service delivery approaches. Despite a drastic health worker shortage, particularly in the rural areas where the majority of the population lives, and the second-highest adult HIV prevalence globally (21.1%)[8] Lesotho has managed to reduce HIV transmission and AIDS-related deaths considerably.[9] This success is based on decentralized HIV testing and care, involving lay village health workers (VHWs) to deliver accessible and equitable services in urban and rural areas alike.[10,11] It has been demonstrated that decentralization and task shifting of healthcare services to lay healthcare workers have the potential to bring services closer to the community and to reduce access

	barriers such as transport costs, travel time and lacking awareness without compromising quality of care, therefore forming the basis for integrated, community-based health service delivery.[12–14] However, current community-based care delivery services in Lesotho and other Southern African countries remain largely fragmented with separate structures for HIV, SRHR and child health and are often largely neglecting NCDs.[15] NCD care is located at health facilities where due to high workload, shortage of staff, lack of specific training and outdated practices, essential services often cannot be delivered adequately. HIV and NCDs are chronic diseases and share several characteristics such as the asymptomatic initial phase, progression to complications with disability and early death, and need for life-long treatment. Integrated service delivery models have the potential to address these jointly, while not only promoting a more efficient and coordinated use of resources but also potentially improving coverage and outcomes of essential health services. Despite its potential, there is only limited evidence on the effectiveness and implementation of community-based integrated health service delivery models in the Southern African context. In the open, prospective ComBaCaL cohort study, we aim to longitudinally investigate the burden of conditions related to NCDs, HIV, SRHR and child health, gaps in essential health service needs, and associated factors in rural Lesotho. Additionally, we seek to generate evidence on community-based, integrated prevention and care approaches to advance UHC in rural Lesotho and similar settings through nested trials. The health service delivery includes (either partially or fully) screening, diagnosis, monitoring, treatment/prevention support, and management for a range of conditions related to NCDs, HIV, SRHR and child health - provided by VHWs in a rural Southern African setting.
Objectives	• To assess the prevalence, treatment rate, control rate and risk factors of conditions of interest and essential health service needs over time in the districts of Butha-Buthe and Mokhothlong, Lesotho • To assess and describe implementation outcomes of VHW-led, community-based data collection and service delivery, i.e. the feasibility, acceptability, appropriateness, resource use, costs, service coverage and quality of data collected and services provided • To assess the effect of the ComBaCaL activities on condition-specific care cascade outcomes, such as screening coverage, disease awareness, and linkage to careTo provide a platform for nested pragmatic trials (Trials within a Cohort, TwiCs) for the assessment of community-based, integrated prevention and care interventions
Cohort variables and implementation outcomes	**Cohort variables** The variables below will be collected at baseline or at the time of a cohort update. Variables which may change over time will be reassessed during follow-up visits at flexible intervals depending on clinical need and requirements of nested trials. Data for these variables are either

	self-reported or retrieved from the personal health booklet, health registries, or obtained through screening tests or follow-up testing. For this protocol version household level data are: o Number of household members. A household member is defined as recognized as such by the head of household or representative. o Geolocation (GPS coordinates) o Socioeconomic indicators (household wealth, food security and healthcare access) For this protocol version individual sociodemographic data are: o Date of birth o Sex o Level of education (>= 10 years) o Income generating activity (>= 18 years) For this protocol version conditions of interest are: o AHT (>= 18 years) o (pre)DM (>= 40 years or >= 18 years and BMI >= 25kg/m^2) o HIV and HIV related conditions o Cervical cancer and pre-cancerous cervical lesions (>= 18 years) o Tuberculosis (People living with HIV (PLHIV) o Pregnancy (females >= 12 years) o Malnutrition (=< 5 years) For this protocol version essential health services are: o Family planning services (>= 12 years) o Maternal health services (>= 12 years and pregnant or recently given birth) o Under-5 child health services (=< 5 years) o NCD prevention (>= 10 years) and care (>= 18 years) o HIV prevention (>= 12 years) and care o Tuberculosis prevention and care (PLHIV & >= 12 years) For this protocol version the following indicators will be assessed: • Individual sociodemographic indicators • Presence of conditions of interest o For aHT, DM and HIV: see diagnostic algorithm in the appendix o Health information and risk factors for conditions of interest o Height, weight and BMI o Abdominal circumference (>= 10 years) o Targeted medical history such as presence of chronic kidney disease, prior stroke, prior myocardial infarction, prior cervical cancer/pre-cancerous cervical lesions, prior TB diagnosis, prior pregnancies and births

	○ Physical activity using the validated International Physical Activity Questionnaire Short Form (IPAQ-SF)[36], which has been adapted to the local context and language according to the IPAQ recommendations[37] (>= 10 years) ○ Diet; using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa[38](>= 10 years) ○ Alcohol, tobacco and other substance use using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[39] and/or the AUDIT-C questionnaire for assessing alcohol consumption or validated questionnaires (>= 10 years) ○ Blood pressure (BP) (>= 18 years) ○ Blood glucose (BG) (>= 40 years or >= 18 years and BMI >= 25kg/m^2) ○ HbA1c (diagnosed with (pre)DM (depending on access to and availability of HbA1c)) ○ HIV risk behaviour assessment using an adapted version of the risk screening tool from Lesotho's national guidelines on the use of antiretroviral therapy for HIV prevention and treatment (>= 12 years) ○ Immunisation status: Assessment of complete or incomplete immunisation status as per Lesotho national immunisation schedule (=< 5 years; for HPV: =< 15 years and female) ○ Under-5 malnutrition screening and growth monitoring: Malnutrition screening and growth monitoring using mid-upper arm circumference (MUAC), weight-for-age growth charts and checking for the presence of pitting oedemas (=< 5 years) • Prevention and care cascade indicators for the essential health service needs and conditions of interest: ○ Screening coverage: number of participants who have been screened (among those who are screening-eligible) for essential health service needs or conditions of interest ○ Condition and health service awareness: number of participants who are aware of their condition of interest or the health services respective to their need(s) ○ Linkage to prevention and care: number of participants linked to prevention and care ○ Engagement in prevention and care: number of participants reporting drug intake for their respective essential health service needs or conditions of interest

	○ Adherence: adherence level of participants being engaged in prevention and care for respective essential health services needs or conditions of interest ○ Met essential health service needs and control level for condition of interest: number of participants who have their essential health service needs met or with controlled conditions of interest (including BP <140/90 mmHg for aHT, FBG < 7mmol/l and/or HbA1C < 7.0% for DM and documented viral suppression for HIV in the last 12 months) • Occurrence of clinically relevant events (see section 7.1) **Implementation outcomes** • Feasibility, acceptability, satisfaction, perceived appropriateness and other implementation outcomes of ComBaCaL activities among participants, VHWs, involved healthcare professionals and further stakeholders using mixed-methods assessments • Coverage indicators, such as number of households visited by VHW, number of individuals monitored by one VHW, number of forms submitted per individual and specific prevention and care service, and number of individuals newly diagnosed with a condition of interest, number of inhabitants refusing ComBaCaL services • Resource use and cost of the ComBaCaL activities, including assessment of time-and-motion data among VHWs • Quality indicators of the ComBaCaL activities, such as completeness of the data collected by VHWs and adherence to clinical algorithms provided via the eHealth application and through quarterly supervisory checks on a randomly selected set of participants to confirm the data accuracy
Study Design	ComBaCaL is designed as an open prospective cohort study enrolling inhabitants of randomly selected villages in the rural areas of Butha-Buthe and Mokhothlong districts in Lesotho. Each cohort village will be managed by a VHW, who lives in the village and is being elected by the village population. VHWs will be supported by a specifically developed eHealth application built on the CHT core framework (referred to for the purpose of this protocol as ComBaCaL app) for data collection and clinical decision-making. The ComBaCaL VHWs in all villages will regularly assess chronic disease indicators and risk factors and offer linkage services if relevant conditions are detected. For an implementation assessment of the cohort activities, metadata analysis of reports submitted via the ComBaCaL app, time-and-motion data, costing data and mixed-methods acceptability, satisfaction and

	perceived appropriateness assessments as well as other implementation outcomes among different stakeholders will be used. In addition to the cohort procedures described in this protocol, we plan to conduct community-based interventions within the ComBaCaL cohort villages in a cohort multiple randomized controlled trials (cmRCT) approach[19] also known as TwiCs. Each TwiC will be submitted separately to the Independent Ethics Committees (IECs) with reference to this protocol.
Inclusion/Exclusion Criteria	Inclusion criteria village level: • Estimated village size of 40 to 100 households • Village consent by village chief • Possibility to recruit and train a VHW from the village population who fulfils the eligibility criteria (outlined in chapter 5.2) Inclusion criteria individual level: • Primary residency in the respective village • Verbal household consent and written individual consent (or guardian consent for children and adolescents below the age of 18 years)
Measurements and Procedures	For the cohort recruitment, all households of selected villages will be contacted by the VHWs in door-to-door visits. Consent will be sought first orally at household level from the household head or his/her representative in case of absence and then in written, electronic form at individual level. At baseline, the variables of interest at household and individual level will be collected by the VHWs. All adult participants will be screened for aHT via standardized screening algorithms using automated BP measurements (see appendix). Adult participants, 40 years or older or having a BMI equal or above 25kg/m^2 will be screened for (pre)DM according to standardized screening algorithms using capillary BG measurements (see appendix). HbA1c levels may be measured in participants diagnosed with (pre)DM (depending on access to and availability of HbA1c). Pregnancy screening will be done using a pregnancy screening checklist and urine pregnancy tests. Participants 12 years or older will be offered an oral HIV screening test for which follow-up testing will be provided by VHW supervisors in case of reactive results. For participants younger than 5 years the mid-upper arm circumference (MUAC) measurements are done using specific MUAC measurement tapes. Growth monitoring will be done using the weight-for-age growth charts provided by the Ministry of Health (MoH). Presence of pitting oedemas will be checked when assessing for malnutrition. Participants with clinical alarm signs or symptoms or any medical condition requiring further diagnostic work-up or treatment will be referred to the closest health facility or the respective district hospital. Follow-up visits by the VHWs will be conducted based on the clinical need and on requirements of nested trials throughout the duration of the study. Clinically relevant events will be documented throughout the duration of the cohort follow-up by the VHWs in dedicated electronic report forms within the ComBaCaL app (see section 7 for definitions).

	To document the process of implementing and maintaining the cohort, we will conduct mixed-methods assessments about the acceptability, satisfaction and perceived appropriateness of the community-based activities among participants, VHWs and involved healthcare professionals at different points in time. 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 VHWs via the ComBaCaL application.
Number of Participants with Rationale	In a first step, we aim to enrol inhabitants of around 100 (range 90-110) randomly selected villages in rural Lesotho. The estimated mean number of inhabitants per village is 200. All inhabitants will be approached for consent and all consenting individuals (assent plus guardian consent for adolescents (10-17 years), guardian consent for children <10 years) will be enrolled into the ComBaCaL cohort. Consent rate is expected to be high (ca. 80%). Thus, the number of cohort members is estimated to be around 16'000. The number of participants was chosen based on available resources and with the aim to allow for meaningful TwiCs for the assessment of community-based chronic disease care delivery strategies.
Study Duration	The cohort will be followed up for at least four years. Cohort follow-up might be prolonged if resources allow.
Study Schedule	First-Participant-In: January 2023 Last-Participant-Out: Mid-year 2027, later if resources for further maintenance of the cohort become available
Study Centre(s)	Scientific lead: Division of Clinical Epidemiology, University of Basel Implementing partners: Ministry of Health Lesotho, SolidarMed Lesotho Study sites: Pre-selected villages in rural areas of Butha-Buthe and Mokhothlong districts in Lesotho
Statistical Analysis incl. Power Analysis	As an open prospective cohort, ComBaCaL aims to provide observational data on conditions and essential health service needs related to NCDs, HIV, SRHR and child health, as well as related risk factors at individual and household level in addition to operational indicators describing implementation aspects of the cohort. A description of the cohort at different time points will be presented using descriptive statistics. Ordinal and binary variables will be presented as counts and proportions with 95% confidence intervals. Continuous variables will be described as medians and inter-quartile ranges and means with 95% confidence intervals. Furthermore, the ComBaCaL cohort will serve as a platform for the implementation of pragmatic TwiCs. These TwiCs, including statistical analysis and sample size calculations will be detailed in separate protocols and submitted for ethics review with reference to this protocol.
Ethical consideration	This project will be carried out in accordance with this protocol and with principles enunciated in the current version of the Declaration of Helsinki[20], as well as all applicable national legal requirements and guidelines. The 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 (NH-REC) of Lesotho. Participation is voluntary, risks are minimal and consent can be withdrawn at any time. The evidence generated in this study aims at informing future national and international clinical guidelines and policies to improve integrated community-based health service delivery in low-resource settings and advance toward UHC. Participants will benefit from improved services in their villages through presence of trained eHealth supported and supervised VHWs. Thus, the ComBaCaL study is likely to have a direct positive effect on health outcomes of participants while generating robust evidence to guide the improvement and scale-up of context-specific integrated care models.

2 BACKGROUND INFORMATION

2.1 NCD burden

Globally, non-communicable diseases (NCDs) are the leading cause of death and disability with a particularly high burden in low- and middle-income countries (LMICs)[1] where more than 75% of all premature NCD deaths occur and where about 80% of deaths are caused by NCDs, resulting in a disproportionate health and socio-economic burden[21]. Arterial hypertension (aHT) is associated with 10.8 million annual deaths globally, mostly in LMICs' rural areas, where treatment rates are below 30%[3–6,22]. There is a lack of scientifically validated pragmatic and scalable prevention and care models in LMICs to make NCD screening and treatment equitably accessible[18]. In sub-Saharan Africa, the NCD burden has risen significantly over the past two decades, driven by the increasing prevalence of cardiovascular risk factors such as unhealthy diets, smoking, insufficient physical activity, aHT, obesity, diabetes mellitus (DM), dyslipidemia, and air pollution[3,4]. It is anticipated that NCDs will overtake communicable, maternal, neonatal, and nutritional diseases combined as the leading cause of mortality in sub-Saharan Africa by 2030[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 (especially TB) as major cause of disability, morbidity and early death[7]. Of the adult population, 22% are affected by aHT and 6% by DM.[1,16]

2.2 Decentralized integrated chronic care and prevention

Extensive evidence shows that decentralization of healthcare services with task-shifting to community-based lay cadres may (cost)-effectively increase access to care and improve health outcomes for a variety of diseases, especially in settings where professional healthcare workforce and financial health system resources are scarce.[12,23–26] Based on these findings, the World Health Organization (WHO) is promoting the strategic integration of community-based healthcare services in existing health systems[27] and the United Nations Programme on HIV/ AIDS (UNAIDS) has launched a plan to recruit 2 million community health workers in Africa to support such a strategy.[28]
Community-based lay health workers are bringing services closer to the community and are reducing access barriers such as transport costs, travel time and lacking awareness. In the spirit of "leave no one behind", community-based care offers more equitable and less stigmatized access to health services than facility-based care thereby advancing progress towards universal health coverage (UHC). In addition, it has the potential to strengthen civil society and create job opportunities in rural areas.[27]

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[15]. Despite a drastic health worker 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%)[29], and the second-highest adult HIV prevalence globally (21.1%)[8], 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 providers to deliver accessible and equitable services for the urban and rural population alike. The HIV programs in rural areas have demonstrated that in Lesotho, healthcare tasks can be successfully decentralized and shifted to lay village health workers (VHWs), who support and act as a link between the community and the clinics to decrease the burden on overwhelmed health facilities. Currently, the community-based healthcare delivery in Lesotho is focused on HIV and maternal and neonatal diseases, largely neglecting other chronic conditions. Furthermore, facility-based services are strained by high workload, staff shortages, lack of specific training and medication stock-outs resulting in persistent prevention and care gaps.

Thus, extending community-based service delivery towards an integrated comprehensive package for conditions and essential health service needs related to HIV, SRHR and child health could present a promising approach to strengthen primary care in Lesotho.

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

We plan to address this gap through a multi-disciplinary research and implementation partnership, the Community-Based chronic disease Care Lesotho (ComBaCaL) program. ComBaCaL aims at establishing and validating a community-based, integrated health service delivery model involving eHealth-supported lay healthcare workers. The ComBaCaL cohort study provides the platform for the scientific assessment of the proposed community-based chronic disease care model through nested trials within cohorts (TwiCs).

3 OBJECTIVES AND PURPOSE

3.1 Objectives

The overall objective of the ComBaCaL cohort study and subsequent nested trials is to assess the impact of community-based, lay-led prevention and care interventions towards UHC in rural Lesotho.
We aim to establish a prospective research and service delivery platform in rural Lesotho that is managed by eHealth-supported VHWs providing regular screening, monitoring and referral services for conditions and health needs related to NCDs, HIV, SRHR and child health. We want to assess implementation outcomes of the cohort as well as the effect of the cohort activities on condition-specific prevention and care cascades. Subsequently, we will develop nested trials to assess the effectiveness and implementation of specific community-based health service delivery interventions.

3.1.1 Specific objectives

- To assess the care cascades – including prevalence, treatment rate, control rate – as well as risk factors of various health conditions and essential health service needs over time in the districts of Butha-Buthe and Mokhothlong, Lesotho.
- To assess and describe implementation outcomes of the VHW-led, community-based data collection and service delivery, i.e. the feasibility, acceptability, appropriateness, service coverage, resource use (including time and motion), costs and quality of the data collected and the services provided.
- To assess the effect of the ComBaCaL activities on condition specific care cascade outcomes, such as screening coverage, disease awareness, and linkage to care.
- To provide a platform for nested pragmatic trials for the assessment of community-based, integrated prevention and care interventions.

3.2 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[7].

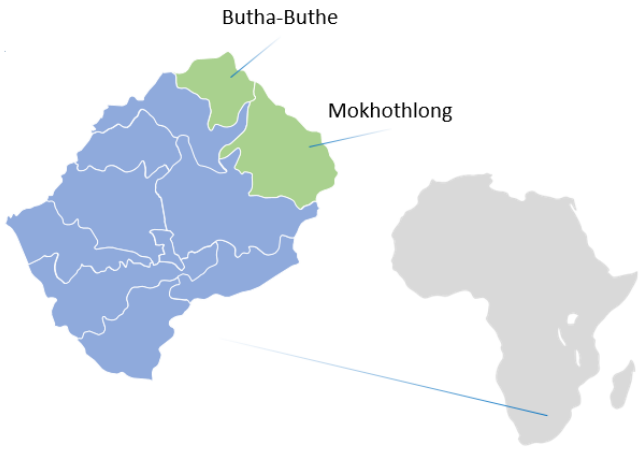

Figure 1 Map of Lesotho with the two districts Butha-Buthe and Mokhothlong

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[15]. The Lesotho VHW program thus represents a meaningful starting point for implementation research on enhancing community-based healthcare 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. The lack of

evidence on integrated, community-based prevention and care strategies that work to support UHC in rural Lesotho is the gap that the ComBaCaL cohort study is aiming to fill and that is justifying the choice for the rural setting in Lesotho where the need for local NCD implementation research has remained unaddressed so far.

4 STUDY DESIGN

The ComBaCaL cohort is an open prospective cohort enrolling inhabitants of randomly pre-selected villages in the rural areas of Butha-Buthe and Mokhothlong districts in Lesotho. At cohort initiation, we will enrol inhabitants of around 100 (range 90-110) villages. Each cohort village will be managed by a VHW, who lives in the village and is being elected by the village population. VHWs will be supported by the specifically developed tablet-based ComBaCaL app for data collection and clinical decision support for screening and diagnosis of conditions related to NCDs, HIV, SRHR and child health. VHWs will be supervised by healthcare professionals of the respective catchment area's health facility and Chronic Care nurses (CC nurses).
The VHWs in all villages will regularly update the cohort census, assess for indicators of our conditions and essential health service needs of interest and their associated risk factors. If required, they will offer linkage and monitoring services for the respective conditions.
For an implementation assessment of the cohort activities, metadata analysis of reports submitted via the eHealth application, mixed-methods acceptability, satisfaction and perceived appropriateness assessments as well as time and motion data and other implementation outcomes among different stakeholders will be used.
In addition to the cohort activities described in this protocol, we plan to assess the effect of community-based chronic disease prevention and care interventions within the ComBaCaL villages in a cohort multiple randomized controlled trials (cmRCT) approach[19,34,35] also known as trials within a cohort (TwiCs). These TwiCs are not part of this protocol but will be submitted separately to the IECs with reference to this protocol.

4.1 Variables of interest

4.1.1 Cohort variables

All cohort variables will be assessed at baseline or at the time of a cohort update. Variables which may change over time will be reassessed during follow-up visits at flexible intervals depending on clinical need and requirements of nested trials.

For this protocol version household level data are:

- Number of household members. A household member is defined as recognized as such by the head of household or representative.
- Geolocation (GPS coordinates)
- Socioeconomic indicators (household wealth, food security and healthcare access)

For this protocol version individual sociodemographic data are:

- Date of birth
- Sex
- Level of education (>= 10 years)
- Income generating activity (>= 18 years)

For this protocol version conditions of interest are:

- AHT (>= 18 years)
- (pre)DM (>= 40 years or >= 18 years and BMI >= 25kg/m2)
- HIV and HIV related conditions (all; people living with HIV (PLHIV))
- Cervical cancer and pre-cancerous cervical lesions (>= 25 years)

- Tuberculosis (PLHIV)
- Pregnancy (>= 12 years)
- Malnutrition (=< 5 years)

For this protocol version essential health services are:

- Family planning services (>= 12 years); including education, pregnancy screening, and comprehensive engagement in contraceptive care.
- Maternal health services (>= 12 years and pregnant or recently given birth); including education, comprehensive engagement in antenatal and postnatal care, timely immunizations, as well as access to and use of preventive deworming and supplements (e.g. iron folate).
- Under-5 child health services (=< 5 years); including education of caregivers, malnutrition screening, growth monitoring, timely immunizations, as well as access to and use of age-appropriate preventive deworming and supplements (e.g. Vitamin A and other micronutrients).
- NCD prevention (>= 10 years) and care (>= 18 years); including education, counselling on CVD prevention, screening and management of NCDs such as aHT, (pre)DM and pre-cancerous cervical lesions/cervical cancer. Adequate prevention of cervical cancer further encompasses timely HPV vaccination for adolescent girls aged 9-15 years.
- HIV prevention (>= 12 years) and care; including education, access to and use of preventive methods (e.g. risk behaviour counselling, condoms or biomedical HIV prevention) and HIV testing. In addition, comprehensive engagement in HIV care entails access to and use of antiretroviral treatment and adherence support, as well as regular screening for opportunistic infections and monitoring of viral load.
- Tuberculosis prevention and care (PLHIV & >= 12 years); including education, access to tuberculosis testing and diagnosis and tuberculosis preventive treatment. Furthermore, engagement in comprehensive tuberculosis care.

For this protocol version the following indicators will be assessed:

- Individual sociodemographic indicators
- Presence of conditions of interest
    - For aHT, DM and HIV: see diagnostic algorithm in the appendix
- Health information and risk factors for conditions of interest
    - Height, weight and BMI
    - Abdominal circumference (>= 10 years)
    - Targeted medical history such as presence of chronic kidney disease, prior stroke, prior myocardial infarction, prior cervical cancer/pre-cancerous cervical lesions, prior TB diagnosis, prior pregnancies and births
    - Physical activity using the validated International Physical Activity Questionnaire Short Form (IPAQ-SF)[36], which has been adapted to the local context and language according to the IPAQ recommendations[37] (>= 10 years)
    - Diet; using a shortened unquantified food frequency questionnaire adapted from an assessment tool for obesity used in South Africa[38](>= 10 years)
    - Alcohol, tobacco and other substance use using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[39] and/or the AUDIT-C questionnaire for assessing alcohol consumption or validated questionnaires (>= 10 years)
    - Blood pressure (BP) (>= 18 years)
    - Blood glucose (BG) (>= 40 years or >= 18 years and BMI >= 25kg/m^2)
    - HbA1c (diagnosed with (pre)DM (depending on access to and availability of HbA1c))

  - HIV risk behaviour assessment using an adapted version of the risk screening tool from Lesotho's national guidelines on the use of antiretroviral therapy for HIV prevention and treatment (>= 12 years)
  - Immunisation status: Assessment of complete or incomplete immunisation status as per Lesotho national immunisation schedule (=< 5 years; for HPV adolescent girls aged 9-15 years)
  - Under-5 malnutrition screening and growth monitoring: Malnutrition screening and growth monitoring using mid-upper arm circumference (MUAC), weight-for-age growth charts and checking for the presence of pitting oedemas (=< 5 years)

- Prevention and care cascade indicators for the essential health service needs and conditions of interest
  - Screening coverage: number of participants who have been screened (among those who are screening-eligible) for essential health service needs or conditions of interest
  - Condition and health service awareness: number of participants who are aware of their condition of interest or the health services respective to their need(s)
  - Linkage to prevention and care: number of participants linked to prevention and care
  - Engagement in prevention and care: number of participants reporting drug intake for their respective essential health service needs or conditions of interest
  - Adherence: adherence level of participants being engaged in prevention and care for respective essential health services needs or conditions of interest
  - Met essential health service needs and control level for condition of interest: number of participants who have their essential health service needs met or with controlled conditions of interest (including BP <140/90 mmHg for aHT, FBG < 7mmol/l and/or HbA1C < 7.0% for DM and documented viral suppression for HIV in the last 12 months)

- Occurrence of clinically relevant events (see section 7.1)

4.1.2 Implementation outcomes

For an evaluation of the ComBaCaL cohort implementation, the following indicators will be assessed:

- Feasibility, acceptability, satisfaction, perceived appropriateness and other implementation outcomes of ComBaCaL activities among participants, VHWs, involved healthcare professionals and further stakeholders using mixed-methods assessments
- Coverage indicators, such as number of households visited by VHW, number of individuals monitored by one VHW, number of forms submitted per individual and specific prevention and care service, and number of individuals newly diagnosed with a condition of interest, number of inhabitants refusing ComBaCaL services
- Resource use and cost of the ComBaCaL activities, including assessment of time-and-motion data among VHWs
- Quality indicators of the ComBaCaL activities, such as completeness of the data collected by VHWs and adherence to clinical algorithms provided via the eHealth application and through quarterly supervisory checks on a randomly selected set of participants to confirm the data accuracy

4.2 Measures to minimize bias

4.2.1 Blinding

No blinding is foreseen for the cohort study.

4.2.2 Measurements

Processes for measurements of clinical outcomes and for the diagnosis of conditions of interest will be standardized and closely supervised. The screening and diagnostic algorithms for conditions such as aHT, DM and HIV (see appendix) will be coded into the ComBaCaL app ensuring that the same measurement procedures and diagnostic criteria will be applied for all participants. All VHWs will undergo a baseline as well as regular refresher trainings with emphasis on correct BP and BG and other measurements as well as interviewing techniques and data entry into the ComBaCaL app. For the provision of oral HIV screenings, the VHWs will receive a 5-day course run by the MoH. Further, they receive individual supervision and mentoring by the CC nurse. Health center nurses and CC nurses will undergo a training adapted to their supervisory tasks. For the duration of the study there will be regular field visits by supervising CC nurses that also include quality supervision reports assessed by the study team to ensure that procedures for data collection are correctly followed by all involved VHWs.

4.2.3 Randomization

No randomization is planned as part of the cohort procedures described in this protocol.
However, the selection of the ComBaCaL villages among all rural settlements in Butha-Buthe and Mokhothlong is done randomly to avoid selection bias. See section 5.1 for details.

4.3 Study duration and duration of participant's participation

The cohort will be followed up for at least four years (48 months). The cohort follow-up may be prolonged beyond the five-year horizon if resources would become available. We plan to enrol first participants in January 2023.

4.4 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to NH-REC and EKNZ for approval before implementation while minor amendments will be submitted to NH-REC only. Protocols of TwiCs nested within the ComBaCaL cohort population will be submitted to both involved IECs with reference to this protocol.

4.5 Withdrawal and discontinuation

4.5.1 Individual level

Participants can withdraw cohort consent at any time without being asked justification. The possibility to re-enter the cohort later through contacting the local VHW will be offered. Data collected until the time of withdrawal will be included in the analysis.
The study team will not discontinue individual participants.
Participants may refuse specific parts of the assessments/screenings at enrolment or follow-up but remain in the cohort study. For example, a participant may refuse blood glucose measurement but agree to the other assessments.

4.5.2 Study and village level

The village chief may request withdrawal of a village via the local VHW. The study team will then get in contact with the village chief to inquire the reasons for the intended withdrawal. 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 withdrawal persists, the data collection for the ComBaCaL study will be stopped in the village while the VHW will continue with the routine activities as part of his/her task assigned by the MoH.

After withdrawal of village consent in one or more villages, the study team may replace withdrawing villages by other villages randomly selected from the list of rural villages not yet included in any other study in Mokhothlong and Butha-Buthe districts (see section 5.1).
If in a village, the 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 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 entire study or certain villages.

The reasons to pause or discontinue the entire study 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 individual villages include the following:

- Insufficient funding to continue the study in all villages
- 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. If the Principal Investigator chooses to terminate or pause the study for safety reasons, he will immediately notify all investigators and subsequently provide written instructions for study termination. Co-investigators may pause the study in certain villages in case of safety concerns without written notice in advance. If Co-Investigators wish to pause or discontinue the study or certain villages, they may address the request to pause or discontinue in written form to the Principal Investigator. Co-Investigators may not pause or discontinue the study or certain villages for other reasons than safety concerns without consulting the Principal Investigator.

4.6 End of project

At the closure of the study or premature termination, all study data will be locked and archived. The electronic database will be locked and a complete study dataset will be transferred to the statistician and the Principal Investigators through a secure channel. The study data will be stored by the Department of Clinical Research (DKF) at the University Hospital Basel on a secure server for a minimum of 10 years and be destroyed thereafter (see section 9.4).

5 SELECTION OF STUDY PARTICIPANTS

5.1 Selection of villages

Participants of the ComBaCaL cohort will be recruited in randomly selected rural villages in Mokhothlong and Butha-Buthe districts in Lesotho. Based on the 2016 Lesotho Population and Housing Census[44], a total of 675 rural village-clusters have been identified in Mokhothlong (321) and Butha-Buthe (354) districts. Villages that were too small and remotely isolated, or were government settlements (e.g. informal mining village or other construction project) or belong to the area that will be flooded due to the construction of the Polihali dam were excluded. Out of the 675 rural villages, 70 (35 per district) were excluded because they were involved in other chronic disease related studies. In particular, 60 (30 in each district) were part of a population-based NCD prevalence survey and burden assessment (NH-REC ID 139-2021) and 10 (5 in each district) are part of the ComBaCaL pilot study (NH-REC ID 176-2021). Out of the 605 (319 in Butha-Buthe, 286 in Mokhothlong) remaining villages, 140 (70 per district) were randomly sampled, stratified by district 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), by a statistician not involved in the study. The 140 villages will be assessed for eligibility applying the following criteria:

Inclusion criteria village level:

- Village size of 40 to 100 households
- Village consent obtained from village chief
- Possibility to identify or recruit a VHW from the village population meeting the following requirements which are largely in line with the criteria of the Lesotho VHW Program Policy:
    - Criteria of the Lesotho Village Health Program Policy[45]:
        - Having primary residence in the village (according to village chief)
        - Having a proven record of trustworthiness in the resident village
        - Having proven ability to maintain confidentiality on public matters
        - Being aged between 20 and 50 years
        - Being able to provide written reports and being able to do basic mathematical calculations
        - Having at least educational level equivalent to high school leaving certificate (Junior Certificate)

    - Additional ComBaCaL criteria:
        - Having the ability and willingness to work with a tablet-based eHealth tool
        - Having good social and communication skills
        - Having the ability and willingness to interact with health professionals and the village population
        - Being able to speak, understand and write in English
        - Having successfully completed the ComBaCaL VHW training including final assessment

5.2 Selection of VHWs

Prior to cohort recruitment, in each ComBaCaL cohort village, one VHW will be appointed. In villages where an existing VHW has the qualifications and capacity to fulfil the tasks associated with the ComBaCaL activities, he/she will be approached for collaboration in the project. In villages, where there is no VHW or where the existing VHW does not have the qualifications or capacity to fulfil the ComBaCaL tasks or where the existing VHW is declining the offer of collaboration, a new VHW will be selected through a participatory process involving the study team, the MoH district health management team (DHMT) and the village population: The study team together with the local DHMT will send a letter explaining the VHW criteria as outlined above to the village committee composed of the chief, the area councillor and existing VHWs if applicable. The village committee will select three candidates among the

village inhabitants meeting the criteria. Among these three candidates, one will be elected to become the VHW by the village population during a community gathering ("pitso").
The selected VHWs will undergo a targeted training covering basic pathophysiological concepts, screening, diagnosis and basic life-style counselling for chronic diseases, such as aHT and DM, as well as technical trainings on the devices and tools used, especially on correct BP and BG measurements and data entry into the tablet-based ComBaCaL eHealth application.
Additionally, VHWs may undergo the standard six-week VHW training as per the Lesotho Village Health Program Policy.[45] ComBaCaL specific activities may be started independent of whether the standard VHW training has been completed or not.

5.3 Recruitment of participants

All households in selected villages will be visited by the local VHW in a door-to-door cohort recruitment campaign. All present household members will be asked for consent to participation in the ComBaCaL cohort study. Details regarding the two-stepped consent procedure are outlined in section 11.3. The number of absent household members will be registered and the VHW will return to all households with absent members within the following days to complete recruitment.
The ComBaCaL cohort is an open cohort. Thus, at any follow-up visit, new inhabitants of the selected villages will be approached for consent and be enrolled into the cohort if consenting while inhabitants moving out of the village or deceased inhabitants will be removed from the active cohort population.

Inclusion criteria individual level:

- Having primary residence in the village (self-reported at time of enrolment)
- Being able and willing to consent to participation or in case of individuals aged below 18 years, a caregiver who provides consent (with participant's assent for adolescents)

6 STUDY PROCEDURES

6.1 General Setting

Measurements and data entry will be conducted by VHWs. The VHWs will be equipped with the essential tools required for condition monitoring in the community (i.e. BP machines, scales, measuring band, glucometers, urine dipsticks, urine pregnancy tests and oral HIV screening tests). They will undergo a theoretical and practical training covering all aspects required for correct data collection and chronic disease screening, diagnosing, referral and counselling services. At every visit, the VHW will screen participants for warning signs and symptoms (such as shortness of breath, severe headache, chest pain, new-onset confusion, impaired consciousness, severely impaired general state of health, prolonged fever or seizures) and pregnant participants and children under five will be screened for age- or pregnancy-specific warning signs (such as vaginal bleeding for pregnant participants or not being able to be breastfed or skin and eyes appearing yellow for under five year old). In case of any danger-sign the participant is referred to the closest health centre. The VHWs will be continuously monitored and supervised by health centre nurses of the respective village's catchment area, mainly through direct interaction during monthly VHW meetings and by CC nurses through field visits, remote interaction via phone calls or messages sent via the ComBaCaL app and through direct contact during the monthly VHW meetings at the health centre.
The VHWs are embedded within the Lesotho MoH VHW program and may during the project period be trained and equipped to provide further routine services in their communities. The supervision of these routine tasks outside the ComBaCaL activities will be provided within the existing VHW framework by health centre nurses and will not be influenced by the ComBaCaL activities.

6.2 Baseline

After recruitment, all variables of interest (see section 4.1.1) at household and individual person level will be collected.
All adult participants will be screened for aHT applying a standardized, evidence-based screening algorithm using automated BP measurements (see appendix). Participants aged 40 years and above or participants aged 18 years and above and having a BMI of equal or above 25kg/m^2, will be screened for (pre)DM applying a standardized, evidence-based screening algorithm using capillary BG measurements (see appendix). Participants not living with HIV and aged 12 years and above will be offered an oral HIV self-screening test; reactive test results will be followed up by the supervising CC nurses using HIV fingerprick blood tests. Female participants between 12 and 49 will be screened for pregnancy using a six-item pregnancy checklist (as described in the WHO family planning provider handbook) and if required receive a urine pregnancy test. Participants, for whom a relevant condition is detected will be referred to the closest health facility or the district hospital for further work-up and treatment.

6.3 Follow-up

6.3.1 Regular follow-up

Follow-up visits will be conducted at flexible intervals. During the follow-up visits, the VHWs will update the variables of interest collected at baseline (see section 4.1.1). In addition, variables newly introduced as part of this amendment will also be collected. Alongside the updates of individual participant's data, the cohort census will be updated through registration of new households or new members of previously registered households as well as removal of emigrated or deceased participants from the active cohort population. During the follow-up, VHWs will inquire about the occurrence of clinically relevant events (see section 7.1) since the previous visit (including screening of the personal health booklet (Bukana), for documentation of respective events). All clinically relevant events will be documented in a dedicated electronic case report form within the ComBaCaL app. All reports of clinically relevant events will be reviewed and validated by the supervising CC nurses and forwarded to the study physician.

6.3.2 Clinical follow-up

In addition to the regular follow-up visits, the VHWs will conduct follow-up visits for conditions and essential health service needs related to NCDs, HIV, SRHR and child health as well as associated conditions of interest according to the clinical algorithms provided in the appendix. These visits entail confirmatory BP and BG measurements for the diagnosis/exclusion of DM and aHT in case of elevated screening values detected at baseline or during regular follow-ups as well as monitoring of participants with established diagnosis of aHT or DM. For HIV, after a reactive oral HIV screening result, trained ComBaCaL study nurses will perform a follow-up finger prick HIV test. SRHR and child health follow-up visits will be conducted if needed.

Furthermore, VHWs will document census updates and clinically relevant events any time during the cohort follow-up when being informed thereof independent of scheduled visits.

6.4 Implementation assessments

For the assessment of satisfaction, acceptability, perceived appropriateness and other implementation outcomes, such as costing data for delivering services or time and motion data of the community-based activities among different stakeholders, questionnaires will be presented via the ComBaCaL application. The questionnaires may be self-reporting (for VHWs and involved healthcare professionals) or will be administered by VHWs or other study staff (i.e. for participants, VHWs or involved healthcare professionals). Additionally, qualitative research approaches, such as focus group discussion or semi-structured interviews may be applied to gather information among participants, VHWs or involved healthcare professionals.

7 SAFETY CONSIDERATIONS

7.1 Definition and documentation of safety outcomes

Clinical event of special interest (CESI)	Clinical event that is consistent with chronic condition complications, such as • Myocardial infarction • Stroke • Symptomatic heart failure • Chronic kidney disease • Diabetic foot syndrome • Peripheral arterial disease • Hypertensive urgency or emergency • Hyperglycemic emergency • Visual impairment or blindness • Peripheral neuropathy • HIV/AIDS-related event • New TB diagnosis Clinically relevant event possibly related to chronic condition treatment, such as • Intolerance reaction against chronic disease medication leading to discontinuation of the medication concerned (including allergic reactions, drug interactions or rare severe side effects such as lactic acidosis)
Serious clinical event (SCE)	Clinical event that: • Results in death • Requires hospitalization ○ Hospitalizations due to uncomplicated delivery are not considered as SCE • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect
Serious clinical event of special interest (SCESI)	SCE consistent with chronic condition complications, such as • Myocardial infarction • Stroke • Symptomatic heart failure • Chronic kidney disease • Diabetic foot syndrome • Peripheral arterial disease • Hypertensive urgency or emergency • Hyperglycemic emergency • Visual impairment or blindness • Peripheral neuropathy • HIV/AIDS-related event • New TB diagnosis SCE possibly related to chronic condition treatment, such as • Intolerance reaction against chronic disease medication leading to discontinuation of the medication concerned (including allergic reactions, drug interactions or rare severe side effects such as lactic acidosis)

VHWs will be trained to screen for and to recognize SCE(SI)s and CESIs and to document them in a dedicated form in the ComBaCaL app.
VHWs may solicit SCE(SI)s and possible CESIs in the following ways:

- Reporting by participants or friends or relatives after inquiry by VHWs during scheduled VHW visits
- Active reporting by participants or friends or relatives outside of scheduled 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 supervisors)
- Clinical observation of VHW during or outside scheduled VHW visit
- Screening of participants' personal health booklets (Bukanas)
- Reporting by staff from health care facilities or other VHWs

Participants, friends, relatives and health centre nurses will be encouraged to notify the VHW about relevant medical events during the cohort follow-up. Many CESIs (i.e. chronic kidney diseases) cannot be recognized clinically without access to further diagnostic tools (i.e. laboratory). For these cases, the VHW will primarily document the results of investigations conducted and diagnosis made by healthcare professionals from entries in the personal health booklet or reports communicated by health centre nurses during the VHW meetings. If needed, the CC nurse may inquire further details at the facilities where the participant was treated for the SCE(SI). On the other hand, the VHW may through her/his continuous presence in the village capture events (i.e. death after stroke or myocardial infarction) that would otherwise remain undocumented.

All SCE(SI)/CESI reports that are submitted by VHWs will be reviewed, validated and if required completed and/or corrected by the supervising CC nurse in the ComBaCaL app within 30 days after submission of the report. Deaths for which the cause cannot be identified by the CC nurse will follow up and gather any additional information that can be obtained.

The SCE(SI)/CESI reports will subsequently be discussed on a weekly basis within the data monitoring team together with the CC nurse related to the report submission and then classified by a physician as SCE other than SCESI, SCESI, CESI or none of the three (if sufficient clinical information for classification is available). If the clinical information available is not sufficient for classification of the case, the responsible CC nurse and/or VHW are asked to collect further data.

7.2 Causality of SCE(SI)s and CESIs

The ComBaCaL cohort study does not entail any intervention other than screening, diagnosing, counselling and referral of participants with relevant conditions as well as other routine VHW tasks. Therefore, a direct causation between the study activities and an SCE(SI) or CESI is highly unlikely. An indirect causation (for example a car accident on the way to the health centre or a drug reaction after prescription of chronic disease treatment after referral) is possible. No causality assessment will be performed for reported SCE(SI)s and CESIs.

7.3 Reporting of SCEs and CESIs

A list of all SCE(SI)s and CESIs will be submitted to the Principal Investigators on a quarterly basis and to the NH-REC along with the yearly reports.

8 STATISTICS

8.1 Determination of sample size

This is an open prospective cohort study and no sample size calculation is performed. In a first step, we aim to enrol inhabitants of around 100 villages. Assuming an average of 200 eligible inhabitants per village and a high participation around 80%, we estimate that we will reach a cohort population of around 16'000 participants. We have secured the funding to pursue a cohort of this size for at least four years.
Sample size calculation for future projects nested in the cohort (e.g. TwiCs) will be detailed within the corresponding sub-protocols.

8.2 General cohort statistics

The variables collected within the ComBaCaL cohort will be summarized using descriptive statistics such as counts, proportions with 95% confidence intervals, medians and interquartile ranges and means with 95% confidence intervals at time point of collection as defined. To establish the prevention and care cascade, proportions will be derived by dividing the number of occurrence of events at a specific stage of the cascade by the population at risk at the corresponding stage.

Statistical methods for future projects nested in the cohort will be part of the corresponding sub-protocols and separate statistical analysis plans.

8.3 Analysis of the ComBaCaL activities' effects on condition specific prevention and care cascades

The ComBaCaL activities with NCD, HIV, HIV related, SRHR and child health related screening and referral services are likely to have an effect on prevention and care cascade outcomes compared to the current standard at community-level. We will conduct a pre-specified analysis to assess the effect of the ComBaCaL activities on condition specific prevention and care cascades.

8.3.1 Hypothesis

VHW-led screening, monitoring and referral services improve care and prevention cascade outcomes for NCDs, HIV, SRHR and child health as well as other associated health conditions and essential health service needs will improve after introduction of the ComBaCaL activities in the respective villages compared to baseline.

8.3.2 Endpoints

Data for all endpoints is either self-reported or retrieved from the personal health booklet, health registries at facilities or ComBaCaL app.

- Screening and service coverages: number of participants who have been screened for the above-mentioned essential health service needs or conditions of interest (see section 4.1.1) will be assessed at several timepoints; 0, 6 and 12 months after enrolment and the introduction of the respective service and at least annually thereafter. Screening coverages are defined as the proportion of screening-eligible participants that have been screened for the respective essential health service need or condition of interest out of the overall number of screening-eligible participants. Service coverages are defined as the proportion of service-eligible participants that have received the respective service. Screenings for conditions of interest specifically also include those conducted at the facility in this timeframe.
- Awareness of the above-mentioned essential health services or conditions of interest (see section 4.1.1) will be assessed at several timepoints; 0, 6 and 12 months after enrolment and the introduction of the respective service and at least annually thereafter. Awareness is defined as

the proportion of participants diagnosed with a condition of interest or eligible for an essential health service who report being aware of their condition or the respective service.

- Linkage to care for the above-mentioned conditions of interest (see section 4.1.1) will be assessed at several timepoints; 0, 6 and 12 months after enrolment and the introduction of the respective service and at least annually thereafter. Linkage is defined as the number of participants with an above mentioned condition of interest who (re)started treatment for their respective condition since enrolment.
- Engagement in care for the above mentioned conditions of interest will be assessed at several timepoints; 0, 6 and 12 months after enrolment and the introduction of the respective service and at least annually thereafter. Engagement is defined as the number of participants with an above-mentioned condition of interest who had a check-up measurement, are taking medication for their condition or reaching control status without intake of medication.
- Level of adherence to drug treatment for the above mentioned conditions of interest will be assessed at several timepoints; 0, 6 and 12 months after enrolment and the introduction of the respective service and at least annually thereafter. Adherence is defined as the number of doses of medication taken within the specified timeframe, which may be the last 7 days, 28 days or more, depending on the appropriate timeframe for adherence evaluation specific to each medication.
- Disease control level for above mentioned conditions of interest will be assessed at several timepoints; 0, 6 and 12 months after enrolment and the introduction of the respective service and at least annually thereafter.. Disease control level is defined as the number of participants with a condition of interest who are reaching condition-specific treatment targets (BP <140/90 mmHg for aHT, FBG < 7mmol/l and/or HbA1C < 7.0% for DM, and viral load <50 copies/ml for HIV).

8.3.3 Statistical methods

We will test for difference in proportion of the different elements of the cascades between the different time points (enrolment to 48 months at least once annually) using chi-square tests or similar statistical methods for comparing proportions. For other analyses such as for nested trials (TwiCs) and analyses beyond the pre-post cascade evaluations, separate statistical analysis plans will be developed.

8.4 Handling of missing data

Missing data might be populated by additional information coming from relevant external registries. Multiple imputations techniques might be used to impute missing adjusting factors in subsequent analyses and will be detailed, if applicable, in the corresponding sub-protocols.

9 DESCRIPTION OF DATA MANAGEMENT

9.1 Specification of source documents

Data collected in the villages will be entered directly into the tablet-based ComBaCaL application by the local VHW. Thus, the electronic forms within the ComBaCaL application serve as source documents in most cases. If required, the VHW may extract clinical data from the patient's personal health booklet or from clinical reports and registers at the health facilities. For participants living with HIV the personal ART number will be collected to retrieve VL results and other measurements from the viral load data base (NH-REC ID 134 2016). Similarly, data might be collected from the registries for NCDs, TB, cervical cancer, PrEP, ANC/PNC, under-five, or family planning. These sources may be important for documentation if participants are not able to provide the exact clinical information. The personal health booklet will always remain with the patient and paper-based or electronic routine clinical reports and registers will remain at the health centres.

9.2 Data recording

All data collected in the villages will be directly entered using the tablet-based ComBaCaL application with regular synchronization to a secure server (hosted at University Hospital of Basel) by trained VHWs. The ComBaCaL app is based on the open source Community Health Toolkit (CHT) Core Framework, the most widely-used open source software toolkit designed specifically for community health systems.[47] Within the CHT Core Framework, a user hierarchy reflecting relevant healthcare cadres and facilities can be configured as well as a variety of tools such as task scheduling, clinical decision support and messaging services. According to the configured user hierarchy, access levels are defined: a VHW will have access to the data collected in his/her village, a health centre nurse will have access to the data of the villages in her/his catchment area and a CC nurse will have access to the data collected by the VHWs she/he is supervising. Adapted to the realities of community-based healthcare delivery, CHT defines a household level between village and individual participants. All individual participants are allocated to a household for which a household head is defined.
Follow-up visits will be prompted as tasks with a due date defined within the ComBaCaL app based on the algorithms encoded. This feature will minimize number of missing visits and enable efficient work planning for VHWs and uncomplicated supervision of pending and upcoming tasks.
Besides the task scheduling, efficient remote supervision is facilitated within CHT through a report validation function and messaging services.

9.3 Confidentiality and coding

The data collected by VHWs and documented in the ComBaCaL app will be used for clinical decision-making, central supervision, programme monitoring and research at the same time. The data collected will be handled with uttermost discretion and only be accessible to authorized personnel who require the data to fulfil their clinical or research duties. Each VHW will have a single, password-protected tablet. Due to the use of the data collected for clinical decision support, contact and clinical data will both be collected in the ComBaCaL app. The app contains a specific contact form capturing personally identifying information such as name, date of birth and contact details for the purpose of identification by VHWs and nurses involved in clinical care. Identifiable data will only be accessible by the respective VHW, the supervising health centre and CC nurse and the study Data Manager overseeing the application's database, and it will not be included in any exported clinical data or metadata. Study participants are automatically allocated a unique participant number, which will be used to identify participants in all data exports containing clinical information. The investigators will respect participants' privacy according to all applicable privacy laws. Only anonymized study data will be published in scientific journals and presented at scientific meetings and conferences. All participants' personal and medical information are confidential and disclosure to third parties is prohibited. Access to identifiable data for the purpose of data quality control may be granted upon request to the Principal Investigators and other members of the study team responsible for data quality control.

9.4 Data security, access, archiving and back up

The study data will be stored on secure servers during the duration of the study in access restricted folders. Participant data will only be accessible to authorized personnel defined by their role. After termination of the study, the database will be locked and the data will remain on secure severs at the University Hospital Basel, where they will be stored for a minimum of 10 years and be destroyed thereafter.

9.5 Data storage on public data repositories

Following the FAIR principles[48], anonymized datasets of cohort analyses will be deposited on an openly accessible data repository, such as zenodo.org[49].

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Supervision

10.1.1 Local supervision and data quality checks

Data will be collected by the VHWs and documented directly in the tablet-based ComBaCaL app. Direct supervision of VHWs and data quality checks will be ensured by two complementary cadres. In the first cadre, routine health centre nurses will provide clinical supervision for the VHWs in their catchment area through a supervisor login of the ComBaCaL app, which will allow them to review data collected and to send messages for queries to individual VHWs. Furthermore, health centre nurses will provide mentoring, training and supervision in monthly meetings at the health centre where VHWs will participate together with other VHWs.

In the second cadre, CC nurses will complement the supervision provided by routine health centre nurses. CC nurses are registered nurses who will be trained specifically on study procedures and on the management of DM, aHT, as well as HIV and HIV-related conditions. Each CC nurse will be responsible for the supervision of around 25 VHWs. The CC nurses will regularly review and authorize the reports uploaded by the VHWs in the ComBaCaL app. Additionally, they will conduct regular field visits in the villages for direct supervision and mentoring of the VHWs, submit supervision reports, and will also be regularly present at the monthly VHW meetings at the health centres where they will provide NCD-specific training and mentoring for health centre nurses and VHWs.

10.1.2 Central data monitoring and quality checks

In addition to the local supervision and data quality checks, regular data quality checks will be run by the study Data Manager on the overall database and anonymized, aggregated data will be shared with the study team for discussion of data quality issues. Queries will be communicated to the respective VHWs either via messages sent within the ComBaCaL app or via the CC nurses.

10.2 Translations - Reference language

The reference language of the study documents is English. Official languages in Lesotho are English and Sesotho. No Sesotho translation will be provided for the study protocol, as all staff of responsible IECs and the study team including the VHWs are literate in English. The electronic patient information and ICFs as well as the paper-based patient information leaflets will be translated from an English master document into Sesotho and provided in both languages. The quality of translation will be ensured by quality and comprehension checks by bilingual individuals not involved in the translation.

10.3 Monitoring and auditing

Members of the Ministry of Health or the NH-REC may visit the research sites. To ensure appropriate organization of the visits, they may inform the principal investigators at least 14 days before the planned visit. Direct access to the source data and all project related files and documents will be granted on such occasions if feasible (access to participant-based personal health booklet might not always be possible). Principal investigators and co-investigators may conduct site-visits, i.e. visiting certain villages to monitor adherence to the study protocol, verify correct conduction of study procedures or clarify uncertainties regarding data quality.

The data management team will conduct regular central monitoring at least on quarterly basis, monitoring data accuracy and completeness, progress in enrolment, adherence to clinical algorithms, occurrence of CESIs, and follow-up visits.

Systematic site visits by external monitors are not foreseen as visiting all 100 villages by external monitors would be resource intensive and because given that all key data are directly collected in the ComBaCaL app source-verification can be done on distance through the central monitoring. However, in case central monitoring should raise concerns or red flags regarding protocol adherence or data quality in specific villages, the investigators may organize external monitoring site visits of these villages.

10.4 Storage of biological material and related health data

Plasma or dried blood spot samples of cohort participants may be collected for storage and future analysis. Samples collected fall under the biobank agreement ("Biobanking regulations, v2.0") approved by the ethics committees in Lesotho and Switzerland. Samples will be stored in biobanks in Butha-Buthe or Mokhothlong districts in Lesotho. Samples may only be exported for analysis after submission and approval of a material transport agreement (MTA) by the NH-REC. No human genome analysis will be conducted on the samples collected. Results of analysis that are relevant for the health of participants will be communicated to participants. Samples will be destroyed latest five years after termination of the study.

11 ETHICAL CONSIDERATIONS

11.1 Independent Ethics Committees (IECs)

This protocol and any protocol amendments, the informed consent form (ICF), and all other forms of participant information related to the study and any other necessary documents 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.

11.2 Risk-benefit ratio

There is no substantial health risk associated with participation in the ComBaCaL cohort. The health condition screening and diagnosis offered will be conducted in line with international recommendations. All participants found to be at risk for a relevant medical condition will be referred to local health facilities for professional work-up and care as per national standard of care.
Data collection will entail questionnaires, automated BP measurements, capillary BG and HbA1C measurements, urine dip stick analysis, urine pregnancy tests and HIV screening tests if clinically indicated. None of the study components have the potential to cause significant harm to participants. The capillary blood collection might cause slight discomfort but no serious complications.
No personalized data of participants will be shared with people other than directly involved study team members if not agreed upon by the participant.
Access to guideline-conform active community-based screening for a range of conditions related to NCDs, HIV, SRHR and child health with linkage services will likely increase early case detection and thus improve access to potentially life-saving treatment. Additionally, regular follow-up with monitoring in the community by VHWs is likely to improve prevention and care for the respective condition for participants compared to standard clinic-based care.
The evidence generated in this study may inform future national and international clinical guidelines to improve care for the previously mentioned conditions 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 the conditions 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 integrated prevention and care delivery on a longer perspective.

11.3 Participant information and consent

In a first step, before the recruitment of VHWs, the study team will obtain oral village consent from the village chief. Thereafter, participant information and consent seeking will be conducted by the local VHW in a two-stepped approach, first on household and then on individual level.

11.3.1 Household consent

When approaching a household, the VHW will first ask whether the household head or a representative is present. If neither the household head nor a representative is present, the VHW will register the household in the ComBaCaL app together with the name of the absent household head if this one is known.
No further information about any household member will be collected on that day, but the VHW will return to the household within the next days to meet the household head to ask for household consent. If the household head or a representative is present, the VHW will inform her/him about the content, risks and aims of the study using digital patient information content on the tablet and ask for oral household consent. It will be mentioned specifically, that participation in the ComBaCaL cohort entails consenting to being randomized for future TwiCs and being included in the control population for analysis without further information or being approached for consent to participate in further community-based interventions. To illiterate household heads, texts will be read out or explained, ensuring that the complete information concerning participation is being transmitted. Ample time will

be given for consideration and all questions regarding participation will be answered by the VHW. The household consent will be documented in the ComBaCaL app by the VHW with a checkbox on the electronic household registration form.

11.3.2 Individual consent

If household consent is obtained, the VHW will inform all present household members about the content, risks and aims of the study using the same digital content as for the household head. To illiterate household members, the text will be read out or explained, ensuring that the complete information concerning participation is being transmitted. The ComBaCaL cohort consent is based on the cmRCT approach, i.e. all cohort participants consent to being randomized as part of a future TwiC. In case they are randomized to the control group, they will not be bothered and data collected as part of the cohort study will be used for the TwiC analysis. In case they are randomized to the intervention group, they will be offered the respective intervention, which they may then accept or refuse. Intervention consent will be asked orally, if the intervention is entailing no other than the task-shifting of procedures recommended by the local guidelines to VHWs (i.e. prescription of first-line aHT treatment by VHW). For all other interventions, written informed consent will be sought. Participants may decline any of the offered interventions without implications on further cohort affiliation. Data of participants declining the intervention, but not withdrawing the cohort consent will be included in TwiC analyses. In the participant information, it will be mentioned specifically, that participation in the ComBaCaL cohort includes consenting to being randomized as part of future TwiCs and to being approached for consent to specific interventions. Ample time for consideration will be given to all individuals. The VHW will make sure that all household members will have the opportunity to ask questions about participation in privacy if desired. Individual consent of household members will be documented with an electronic signature of the participant on the study tablet. Illiterate participants will confirm informed consent by drawing a cross in the electronic signature field, countersigned by an impartial witness (may or may not belong to the household).

To children and adolescents under the age of 18 years, the same content will be explained in an age-adapted manner. Written consent will be sought from a guardian aged 18 years or above together with written assent for adolescents aged 10 to 17 years. No written assent will be sought in addition to the guardian's consent for children below 10 years.

For every household at least one paper-based participant information leaflet will be provided containing all relevant information about study participation as well as contact details of the responsible study staff and representative of the NH-REC to be contacted in case of questions or concerns related to participation.

11.3.3 Withdrawal on household or individual level

Consent can be withdrawn any time on individual or household (by household head) level without justification. Anonymized data collected until the time of withdrawal will be retained in the database.

11.3.4 Service delivery for people declining consent

The VHW will offer the same chronic disease screening and linkage services applied within the study also to inhabitants of the village declining consent to be part of the ComBaCaL main cohort. The data of people not giving consent will not be entered in the ComBaCaL app, but only communicated orally to the individual and noted in the individual's personal health booklet if desired. By not entering the data in the ComBaCaL app, the clinical decision support for diagnosis will not be available to people declining consent, which might limit the quality of services provided.

11.4 Participant confidentiality

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

11.5 Participants requiring particular protection

This study has a strong service delivery aspect as the data collected enables case finding and monitoring of the targeted diseases in the study population. Often people with mental or physical conditions impairing capacity for informed consent are particularly vulnerable to the targeted health issues and conditions. Therefore, we will offer participation to people with impaired judgement and include them in the ComBaCaL cohort if a guardian provides consent. The incapacity to give informed consent together with the reason will be documented in the electronic ICF together with the guardian's electronic signature (or cross with signature of an impartial witness for illiterate guardians). The same services without the clinical decision support of the ComBaCaL app will be offered to people not capable of giving informed consent for whom no guardian consent is obtained.

11.6 Participant compensation

No compensation will be paid for participation in the study.

12 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 Division of Clinical Epidemiology of the University of 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.

13 DISSEMINATION OF RESULTS AND PUBLICATION POLICY

13.1 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 an open-access peer-reviewed journal. The current version of the International Committee of Medical Journal Editors (ICMJE) recommendations is applicable regarding authorship eligibility.[50] The use of professional writers is not intended.

13.2 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.

14 APPENDIX

14.1 Screening and diagnosis of aHT

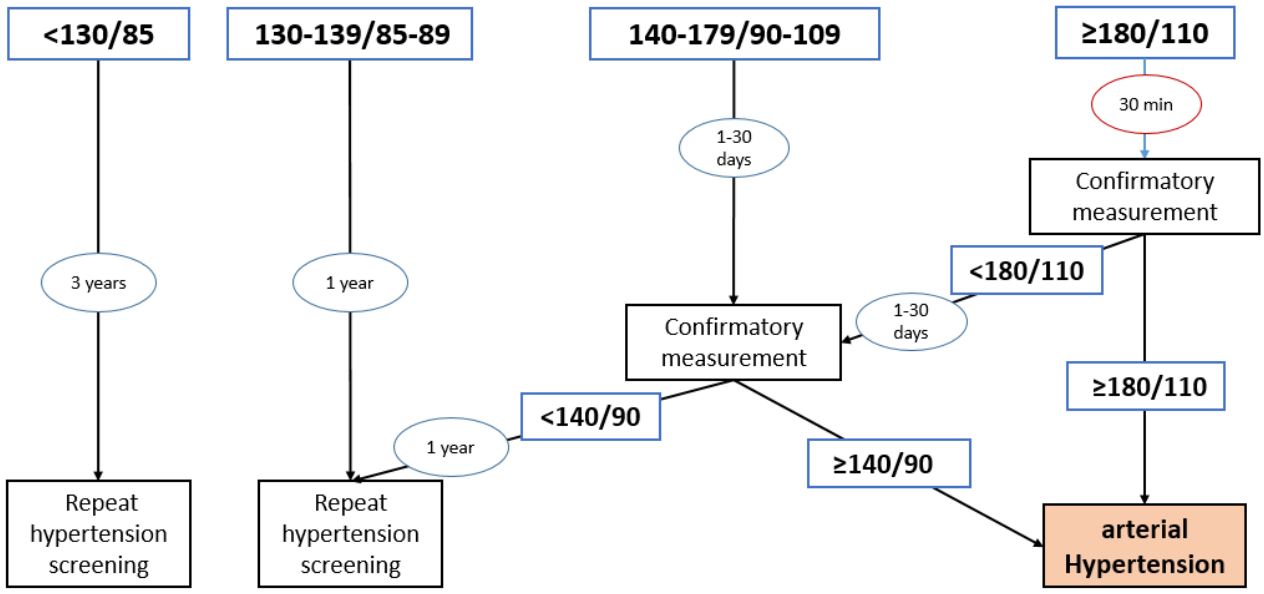

Figure 2 Screening and diagnosis algorithm for aHT

For the determination of BP, standard operating procedure based on the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines 2018[51] and the 2020 Global Hypertension Practice Guidelines of the International Society of Hypertension[52] will be applied using automated BP machines (Omron M3 Comfort [HEM7131-E][53,54]. BP measurements are taken after determination of the correct cuff size in a sitting position after 5 min of rest with feet on the floor, the arm supported without talking or moving during the measurement. At the first visit, the reference arm is determined by measuring BP on both arms. The arm with higher systolic BP is identified as reference arm and used for all subsequent BP measurements. The BP value used for the screening and diagnosis is calculated as the mean value of the last two out of three consecutive measurements at intervals of one minute.

For diagnosis of aHT, two elevated measurements in the range of 140-179/90-109 mmHg on two different days are required or two measurements of 180/110 mmHg or higher on the same day, 30 minutes apart.

14.2 Screening and diagnosis of (pre)DM

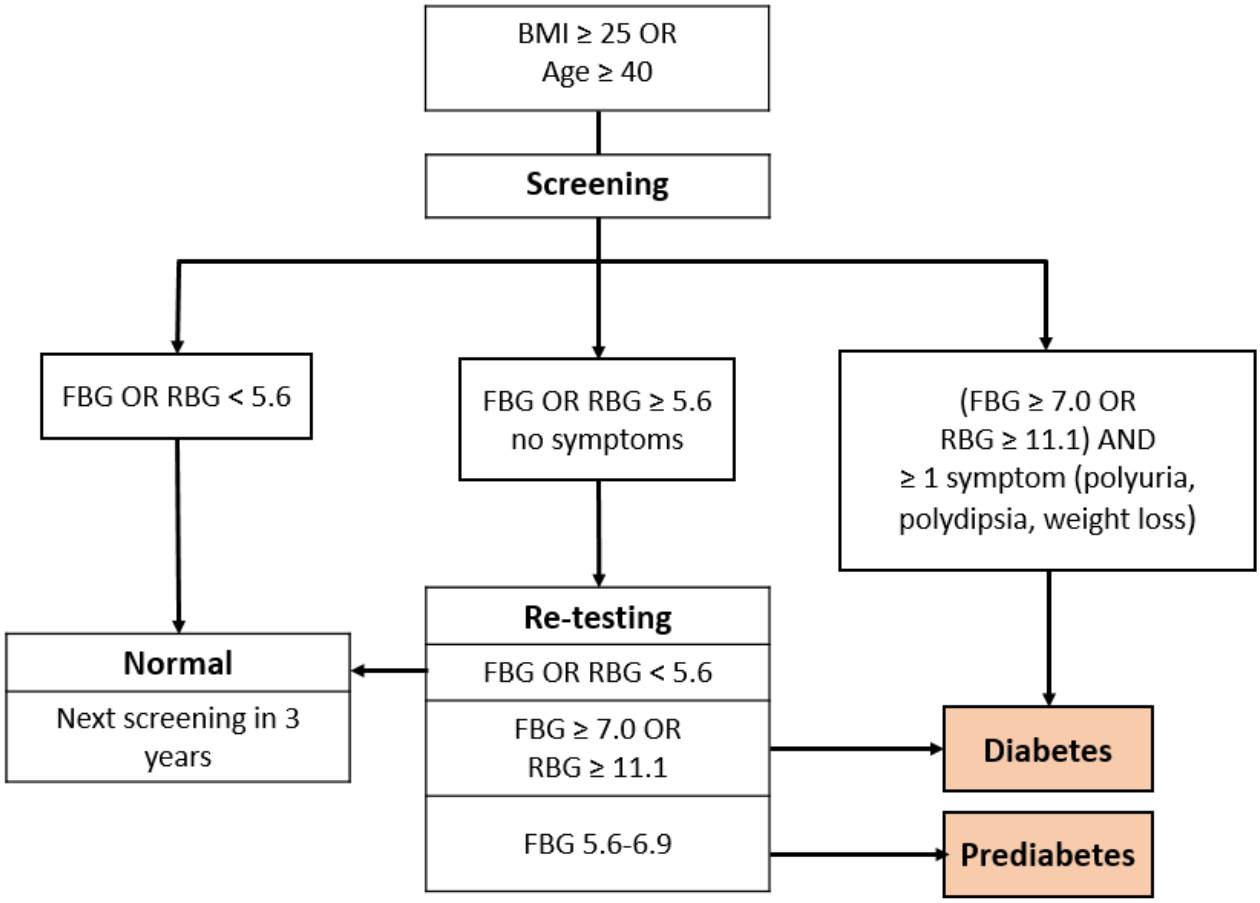

Figure 3 Screening and diagnosis algorithm for (pre)DM. BG: Blood glucose, FBG: Fasting blood glucose, RBG: Random blood glucose.

All adult individuals equal or above 40 years of age or with a BMI equal or above 25kg/m^2 will be screened for (pre)DM using random (RBG) or fasting (FBG) capillary BG measurements. In patients with an FBG or RBG below 5.6 mmol/l, DM can be excluded and the next screening is recommended in three years. Patients with a BG level in the diabetic range (FBG ≥7 mmol/l or RBG ≥11.1 mmol/l) with at least one cardinal symptom of uncontrolled DM (polyuria, polydipsia or weight loss) fulfill the diagnostic criteria for DM. For patients with an elevated BG level, not fulfilling the diagnostic criteria for DM, a confirmatory measurement is required for diagnosis of DM or preDM. The diagnosis of DM is made if the confirmatory measurement is in the diabetic range. PreDM is diagnosed if the FBG is between 5.6 and 6.9 mmol/l. Patients with an FBG or an RBG value in the diabetic range presenting with all three cardinal symptoms of DM (polyuria, polydipsia or weight loss) will be assessed for ketonuria using urine dip sticks. In case of relevant ketonuria (defined as level 3 or more on a 5 level scale), patients will be immediately referred to a higher-level health facility as they may need admission, insulin treatment and close monitoring.

14.3 HIV Testing Algorithm

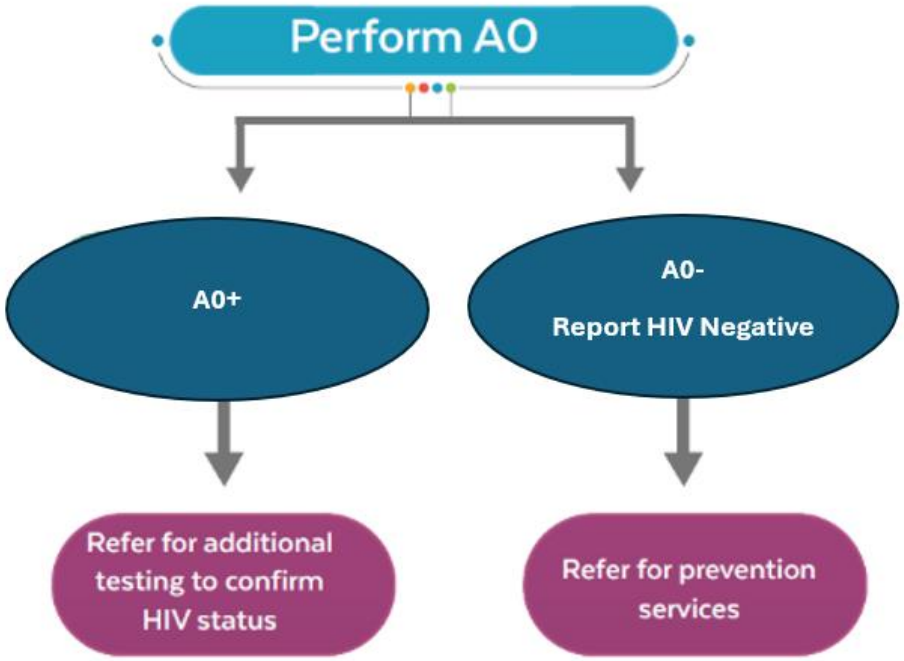

Figure 4. Lesotho strategy for screening and test for triage (adapted from Lesotho National Guidelines)

At the community level, VHWs will perform HIV screening (A0) using an oral HIV screening test (OraQuick®). Reactive screening results will be referred for follow-up and confirmatory testing, either conducted by trained ComBaCaL study nurses or trained ComBaCaL study nurse assistants at the community level using fingerprick blood tests (see Figure 5) or at the health facility or outreach services.

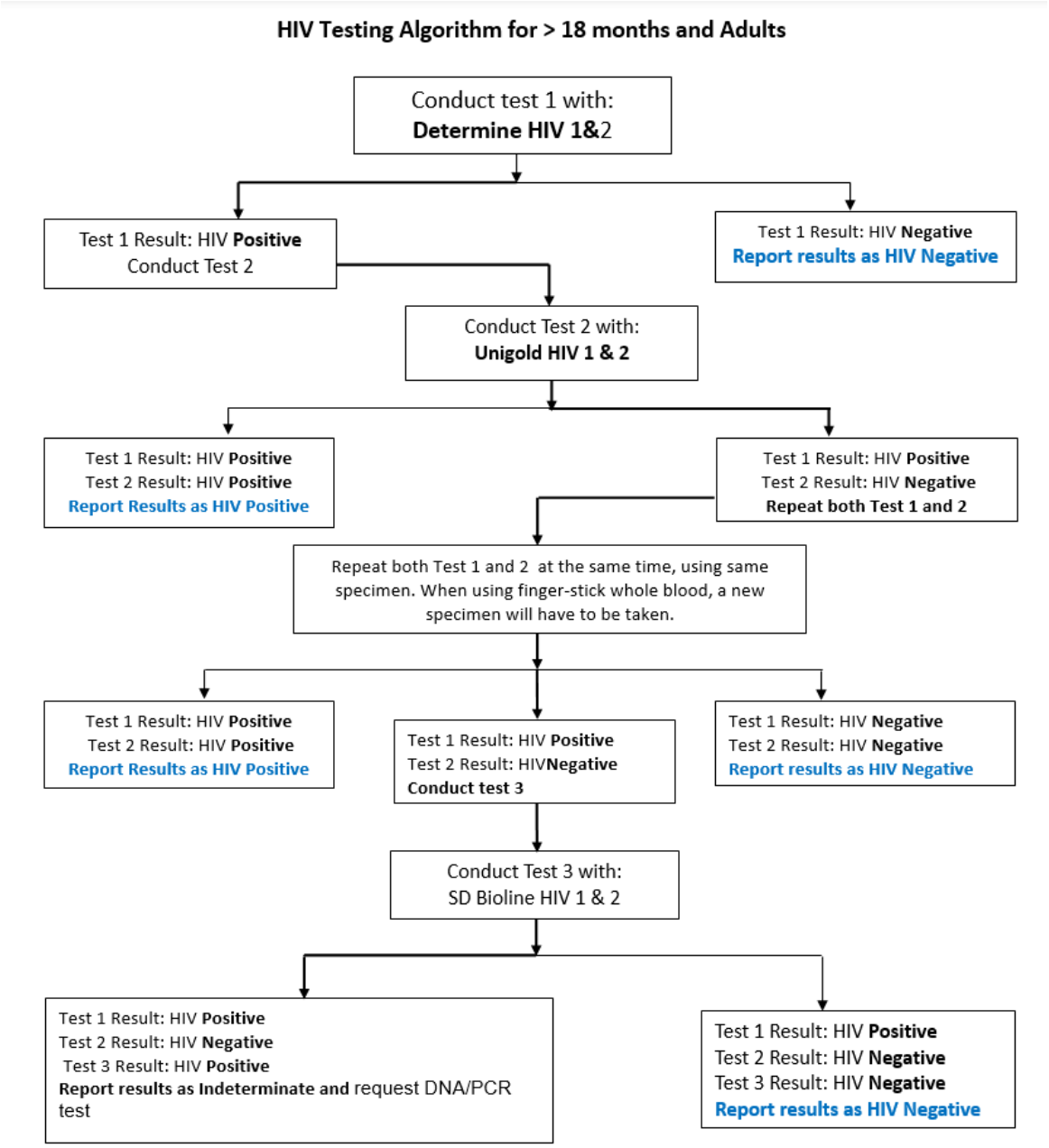

Figure 5. Lesotho national HIV diagnostic testing algorithm for individuals ≥18 months (source Health Research and Laboratory Services Lesotho)

Diagnostic testing begins with Test 1 (Determine™). Individuals with a non-reactive result are reported as HIV negative. Those with a reactive Test 1 result undergo additional testing using Test 2 (Uni-Gold™). A second reactive result requires confirmatory fingerprick testing by second healthcare provider.
If Test 1 and Test 2 results are discordant, both tests are repeated on the same specimen (or on different specimens if not feasible). Persistently discordant results require a third tie-breaker Test 3 (Bioline™). Individuals whose results remain inconclusive after three tests are classified as *indeterminate* and require HIV DNA/PCR testing or confirmatory fingerprick testing by a second healthcare provider. Individuals with non-reactive results after discordance resolution are reported HIV negative.

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