Community-Based Chronic Disease Care Lesotho (ComBaCaL): Protocol for a prospective open pilot cohort (ComBaCaL Pilot)

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO).
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A

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GLOSSARY OF ABBREVATIONS

AE	Adverse Event
ART	Antiretroviral Therapy
BMI	Body Mass Index
BP	Blood Pressure
CCW	Chronic Care Workers
cmRCT	Cohort multiple randomized controlled trial
ComBaCaL	Community Based chronic disease Care Lesotho
COSC	Cambridge Overseas School Certificate
DHMT	District Health Management Team
DM	Diabetes mellitus
FGD	Focus group discussions
FBG	Fasting blood glucose
GRAMMS	Good Reporting of A Mixed Methods Study
HIV	Human Immunodeficiency Virus
HH	Household
HTN	Hypertension
HCTZ	Hydrochlorothiazide
ICF	Informed consent form
KII	key informant interviews
LHW	Lay Health Worker
LMIC	Low and Middle-Income Countries
NCD	Non-Communicable Disease
NHREC	National Health Research and Ethics Committee of Lesotho
PI	Principal Investigator
POC	Point of Care
RFG	Random Blood Glucose
(S) AE	(Serious) Adverse Events
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Swiss TPH	Swiss Tropical and Public Health Institute
TB	Tuberculosis
VHW	Village Health Worker
WHO	World Health Organization

1. BACKGROUND AND PROJECT RATIONALE

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 for these countries[2]. For example, arterial hypertension (HTN) is associated with 10.4 million annual deaths globally, mostly in LMIC rural areas, where treatment rates are below 30%. There is a lack of scientifically validated pragmatic and scalable prevention and care models in LMICs to make NCD screening and treatment equitably accessible. 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, reduced physical activity, HTN, obesity, diabetes mellitus (DM), dislipidaemia, 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[5].

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, and as main barrier for economic development[5]. Of the adult population, 22% suffer from HTN, 6% from DM, and 5% from depression[1,6]. Due to social and economic determinants of health, women are often most affected by difficulty accessing NCD prevention and care[5].

Despite a drastic health workers shortage in Lesotho (0.9 doctors and 10.2 nurses per 10,000 inhabitants, particularly in the rural areas where the majority of the population lives (77.6%)[7], and the second-highest adult HIV prevalence globally (22.7%)[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 health 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 health care provision tasks can be successfully decentralized and shifted to lay health workers (LHWs), who support and act as a link between the community and the clinics to decrease the burden on overwhelmed health facilities. LHWs also bring services closer to the community and reduce access barriers such as transport costs, travel time and community members 'lack of awareness for available services. In the spirit of "leave no one behind", community-based care also offers more equitable and less stigmatized access to health services than facility-based care. In addition, it has the potential to strengthen civil society and create job opportunities in rural areas. World Health Organization (WHO) therefore endorses community-based service delivery and 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[9].

Currently the community-based health care delivery structures in Lesotho are focused on HIV and maternal and neonatal diseases, largely neglecting the management of NCDs. Thus, NCD screening, diagnosis, management and prevention education are located at the clinics. However, due to high workload and shortage of healthcare professionals, active screening of asymptomatic patients for DM and HTN is not possible there.

HIV and NCDs share several characteristics, such as the asymptomatic initial phase, progression to complications with disability and early death, and typically the need for life-long treatment. The Ministry of Health (MoH) of Lesotho has therefore proposed in its NCD strategic plan that lessons learnt from HIV programs should be incorporated into NCD care and that delivery platforms should provide integrated HIV/NCD services[10]. 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[11,12]. To our knowledge, no studies have been conducted or policy documents developed on how to provide pragmatic and scalable prevention and treatment models for NCDs in the context of a high communicable disease burden in Lesotho.

Since 2018 our Basotho-Swiss-research consortium (MoH, Swiss TPH, SolidarMed) has successfully established research projects in the field of decentralized community-based care and eHealth. Building on this experience, we plan to tackle the growing NCD pandemic through a multi-disciplinary research and implementation partnership, the Community-Based chronic disease Care Lesotho (ComBaCaL) program. ComBaCaL aims at establishing and validating a large-scale community-based NCD care model, with the following components: i) decentralized NCD care through lad cadre, Chronic Care Workers (CCWs); ii) e-Health-assistance to monitor patients in the community and at the facility; iii) model self-sustainability through social enterprise; iv) creation of free, generic training materials for NCDs and the community-based model as well as monitoring and empowerment/professional development tools.

To assess the impact on health outcomes of the above-mentioned activities of the ComBaCaL initiative, they will be monitored within a prospective open cohort trial, referred to as the "ComBaCaL main cohort." The aim of the ComBaCaL main cohort is to provide high-quality evidence on village-based, Chronic Care Workers (CCW) NCD service delivery strategies. CCW are trained lay cadres from the community that will be working on the basic management of selected chronic diseases. As it will entail conceptually and logistically challenging activities, we will first set-up a smaller ComBaCaL pilot cohort, with the aim to test implementation procedures in real-world field conditions before beginning the ComBaCaL main cohort. The here-presented study protocol outlines the ComBaCaL pilot cohort assessing the establishment and follow-up of an NCD-focused open community-based prospective cohort, managed by eHealth-supported CCWs. Implementation procedures will be evaluated in mixed-methods assessments addressing all stakeholders of the pilot cohort. Based on the results of this pilot cohort study, the ComBaCaL main cohort will be adapted.

2. PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

ComBaCaL hypothesizes that NCD care in Lesotho and similar low-resource settings could be significantly improved by shifting tasks such as screening, diagnosis and basic management from facility-based health professionals to eHealth supported CCWs within the village or community.

The overall goal of the ComBaCaL pilot cohort, is to inform the design and implementation of the subsequent ComBaCaL main cohort.

The objectives of this pilot cohort are:

1. To establish an observational open NCD-focused cohort in ten villages in Butha-Buthe and Mokhotlong districts in Lesotho that will be managed by trained and supervised CCWs who are supported by a tablet-based eHealth application.

2. To assess the prevalence of common NCDs and associated risk factors in the pilot cohort population and to monitor their development over time. Initial focus will be on HTN, DM, common cardiovascular risk factorsand psychosocial functioning. Other pathologies might be included at a later stage only after submission to the ethics committee in separate amendments.
3. To prepare the pilot cohort as a platform to test the implementation of pragmatic health interventions, which will each be submitted to ethics committees as separate amendments before execution.
4. To assess the implementation procedures of the pilot cohort, including recruitment, training, and supervision of CCWs, functioning and usability of the eHealth application, communication, and interaction between study stakeholders (CCWs, participants, and local health care professionals), enumeration of participants within catchment areas, and subsequent longitudinal data collection.

2.3 Project design

The ComBaCaL pilot cohort has the primary objective to inform the design and implementation procedures of the ComBaCaL main cohort, which will be deployed in the same setting at a later stage. Thus, the choice of study design of the here presented ComBaCaL pilot cohort is closely interlinked with the planned design of the ComBaCaL main cohort. With the ComBaCaL main cohort, we aim to assess lay cadre-led, village-based NCD care strategies. The chronic nature and slow evolvement of the targeted diseases such as HTN and DM require a longitudinal design to assess the effect of tested preventive and therapeutic interventions. We plan to evaluate different community-based care delivery strategies in pragmatic, controlled interventions. Based on the requirements for longitudinal observation and pragmatic comparison between different care models, we plan to design the ComBaCaL main trial as a cohort multiple randomized controlled trial (cmRCT). A cmRCT entails the initial recruitment of an observational prospective cohort, out of which participants will be randomly sampled for multiple interventions over time. As the ComBaCaL pilot cohort is designed to inform the upcoming main cohort. It will serve as a platform to observationally study (using mixed-methods) implementation procedures and health interventions. The pilot CCWs and village-clusters will, however, not be part of the main ComBaCaL cohort. Five village-clusters will be established in Butha-Buthe and five in Mokhotlong. All ten clusters will be from rural areas in the catchment areas of hospitals and health centers and will be randomly selected from the overall ComBaCaL village-cluster list established before commencement of the pilot cohort.

3. PROJECT POPULATION AND RECRUITMENT PROCEDURES

3.1 Project population, inclusion and exclusion criteria

The ComBaCaL pilot cohort participants will be recruited from the ten villages in Butha-Buthe and Mokhotlong districts in Lesotho (five villages in each district).

Inclusion criteria on cluster-level are defined as follows:

- Village situated in Butha-Buthe and Mokhotlong districts in Lesotho
- Five villages per district in rural areas (as defined by Lesotho Census List)
- Consenting village chief and area councillor
- Possibility to recruit a CCW from the village population who meets the criteria listed below

As the primary goal of the ComBaCaL pilot cohort is the assessment of implementation procedures, the involved CCWs will be asked to share their experiences in qualitative interviews,

scheduled surveys distributed through the eHealth app, and contextual inquiries. Thus, they fulfil a double role in the pilot cohort: implementing the study in the villages and participating as study subjects themselves.

Inclusion criteria for the CCWs are defined as follows:

- Living in the chosen pilot cohort cluster-village
- Should not be a Village Health Worker (lay cadre already working in the community under the MoH)
- From 25 to 55 years old, or married if under 25 years
- Must be able, and willing, to access the nearest facility (either walking or public transport) and to walk around her/his village.
- Is not employed at the time of recruitment
- Is unlikely to leave the village cluster within the coming year
- Is available to support study participants and willing to support study participants outside of traditional working hours (evenings and weekends)
- Elected by the village population through village gathering (pitso)
- Literate in English and Sesotho
- At least educational level equivalent to secondary school certificate
- Ability and willingness to work with a tablet-based eHealth tool
- Good social and communication skills
- Ability and willingness to interact with health professionals and the village population
- Willingness to participate in social economic enterprise
- Willingness to participate in the research aspect of the study (answering questions about their experience and perceptions)

All consenting inhabitants of the pilot cohort villages will be enrolled into the pilot cohort. Many NCD risk factors such as overweight or unhealthy diet affect adults and children alike and are often transmitted from one generation to the next within families. To assess the prevalence of NCD risk factors in the whole population and to understand their evolution throughout childhood, adolescence and adulthood, we will enrol children of all ages into the cohort. The enrolment of children into the cohort will only entail observational data collection.

The only exclusion criteria for participants are not having a main residence in one of the pilot cohort villages or not consenting to participate in the cohort.

Mixed-methods implementation assessments and health interventions that will be conducted within the pilot cohort might have more specific individual-level inclusion/exclusion criteria that will be specified in respective separate protocol amendments.

3.2. Recruitment, screening and informed consent procedure

3.2.1. Recruitment, training, and remuneration of CCWs

CCWs will be recruited at selected pilot villages through a community gathering (“pitso”). The local village chiefs and the area councilor will be contacted personally, informed about the content and objectives of the ComBaCaL pilot study and asked for consent for participation of the village. Subsequently, a letter will be sent to consenting village chiefs and local councilors specifying the requirements for a CCW with the request to organize the pitso to elect the local CCW. The village committee composed of the chief, area councillor and VHW will select 3 candidates within the village. Once the 3 candidates are selected by the village committee, there will be a pitso for villagers to select one candidate among the 3 candidates to be a CCW.

The aim is to recruit individuals as CCWs that comply with the above listed requirements and that have a good standing and high trust within their community. Besides election of the CCW, information about the ComBaCaL pilot cohort will be provided to attending community members during the pitso.

Once selected, CCWs will receive an extended training facilitated by the PI, health center nurses and or nurse on:

a) pathophysiology, screening, diagnosis and basic management of NCDs with main focus DM and HTN
b) eHealth supported medical history taking including screening for clinical alarm symptoms, cardiovascular risk factors, screening for drug-related adverse events and drug-toxicities, with focus on first-line drugs for DM and HTN
c) lifestyle health education
d) basic clinical examination including BP, weight and blood glucose measurement
d) understanding of the clinical algorithm for management and for referral in case of clinical deterioration of their participants,
f) mental health and psychosocial functioning assessment
g) basics of good clinical practice, including consent seeking and keeping confidentiality
h) performing basic data entry/management within dedicated eHealth tool

The CCWs will receive continuous monitoring by the PI, a qualified nurse and the study physician, and are additionally supported by supervisory staff from the nearest health facility and District Health Management Team (DHMT). Depending on PI observation or CCWs needs for more training, the refresher training sessions will be organized whenever needed.

The CCWs will be provided with the tablets, BP machine, urine-dip sticks, glucometer, lancets, sharp containers, informed consent forms and other study documents. CCWs will receive a regular stipend to cover transport reimbursement to their catchment area health facilities and other related costs. The exact amount of the stipend will depend on the workload but range between 1000 and 1500 LSL (60 to 90 Swiss Francs) per month. All the CCWs will receive an airtime voucher in order to stay in close contact with their responsible supervisory staff and PI, and data bundles for study tablets with the eHealth tools.

3.2.2. Recruitment of Participants

The CCW will do regular rounds (every 3-9 months) in his/her village, visiting all households. The spectrum of activities may differ between rounds. The initial round will serve to censor the village households and household members and to enroll consenting villagers into the cohort. First, oral consent from the head of household will be sought to enter the household and to enumerate all household members. Second, all household members will be informed about the content, risks and objectives of the ComBaCaL pilot cohort. All household members will be informed about the observational nature of the pilot cohort as well as about the possibility that they might be approached for voluntary participation in health interventions in the future. They will be given ample time for consideration and the opportunity to ask questions about the study before individual written consent to participate in the cohort will be sought. For household members under 18 years old or incapable of judgement, written consent from the caregiver will be sought.

Persons unable to write can provide consent with a thumbprint, together with the confirmatory signature of a witness other than the CCW.

Number of absent household members will also be registered. The CCW will return to all households with absent members in the following days to complete consent seeking as described above.
For household members declining consent, only gender and age will be registered, but no additional personal or clinical information. No payments will be offered to participants.
The ComBaCaL pilot cohort operates as an open cohort. Thus, at any follow-up visit, new inhabitants of the village will be approached for consent and enrolment into the pilot cohort according to the procedures above.

4. STUDY PROCEDURES

4.1 Procedures at first encounter

After consent is obtained from participants, the following data will be collected at baseline using the dedicated tablet-based eHealth application:

Household data

- Household GPS
- Date of Household Visit
- Name and phone numbers of Household head
- Number of present and absent Household members
- Socioeconomic situation and health seeking behavior

Individual HH members data

- Name,
- Birth date,
- Sex,
- Phone numbers,
- Modifiable cardiovascular risk factors (smoking status, alcohol consumption, physical activity, dietary habits)
- Height,
- Weight,
- Medical history (previous and current relevant medical diagnosis including HIV status, current medication, allergies, family history of relevant medical diagnosis),
- Current medical condition and symptoms.

4.2 Screening for chronic conditions

In an initial phase of the study, screening for the following conditions is planned. In the future, further conditions for example mental health will be included and submitted as amended protocols

1. Screening and diagnosis for HTN
2. Screening and diagnosis for DM
3. Screening for mental health and psychosocial functioning

4.2.1. Screening for HTN

Using validated standardized automated BP measurement devices (omRon), BP will be recorded for all participants aged 18 years and above. For the determination of BP, we use a standard operating procedure based on the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines 2018 [13]. BP measures are taken in sitting position after 5 min of rest with feet on floor; back supported; no caffeine, exercise, or smoking in the 30 min before measurement; no talking during measurement; and arms supported (e.g., on table). At the first visit, the reference arm is determined by measuring BP on both arms. The reference arm (with higher BP) is noted in the App and used for all further BP measurements. Thereafter, BP will be measured three times on the reference arm and the average of the last two measurements is calculated. If this average value is below 140/90 mmHg, participants will be classified as not having HTN. If the value is between 140-179/90-119, the BP will be measured again on another day according to the above-described procedures within the next fourteen days. If the value remains in this range, the diagnosis of HTN is confirmed.[13] Diagnosis and grading of HTN will be based on the thresholds provided in the ESC/ESH guidelines 2018 [13] (see table below)

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

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BP = blood pressure; SBP = systolic blood pressure.
[a]BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
[b]Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
The same classification is used for all ages from 16 years.

In participants with a systolic BP value of 180/120mmHg or above, the measurement will be repeated after 30 minutes of rest in a quiet environment. If thereafter, the values remain above 180/120mmHg, diagnosis of HTN is confirmed.

4.2.2. Screening for DM

DM screening will be conducted in a stepwise risk-based approach: participants with symptoms indicative of elevated blood sugar levels (polyuria, polydipsia, weight loss), participants with an elevated risk for DM based on medical history (personal history of HTN, dyslipidemia, cardiovascular disease, gestational diabetes, family history of DM, report of any previous elevated FBG, RBG or HbA1C, given birth to child > 4100 gr) or participants with a BMI above 25 or age

above 40 years will be offered a blood sugar measurement. If participants report no calorie intake in the last eight hours, the measurement will be interpreted as fasting blood glucose (FBG), otherwise as random blood glucose (RBG). If FBG is ≥ 5.6 mmol/l or RBG ≥7 mmol/l, a urine dip-stick stick will be performed and a date will be set for a confirmatory FBG in the days to come. If the confirmatory FBG is between 5.6 and 6.9 mmol/l, participants will be classified as having impaired fasting glucose (IFG). If the confirmatory FBG is 7mmol/l or above, DM is diagnosed. In those diagnosed with DM, a dry blood spot will be collected for determination of glycosylated haemoglobin (HbA1c). Further, in some villages, assessment of HbA1c with point-of-care machines will be piloted.

Participants with symptoms of uncontrolled DM (polyuria, polydipsia and weight loss) and an FBG ≥ 7.0 mmol/l or an RBG of ≥ 11.1 mmol/l and marked ketonuria on the urine dipstick will be referred to the district hospital immediately.

4.2.3. Screening for mental health and psychosocial well-being

Given the high comorbidity of poor mental health and psychosocial functioning with other NCDs, participants will undergo a brief assessment battery to assess relevant domains including psychological distress, quality of life, coping, social support, and intimate partner violence. Psychological distress will be assessed using the General Health Questionnaire (GHQ-12)[14], a 12-item scale assessing various symptoms over the past 4 weeks including concentration difficulties, loss of sleep, feeling stressed, ability to enjoy daily activities, ability to cope, and feeling worthless. This measure has been used extensively in LMIC and recommended as one of the best screening tools for psychological problems in these settings[15].

Quality of life will be assessed using the WHO's Disability Assessment Scale (WHODAS 2.0)[16]. It is a 12-item questionnaire that assesses impairment in the following domains over the past 30 days: cognition, mobility, self-care, getting along with others, life activities, and participation. Total scores are used, with higher scores indicating greater disability.

Social support will be assessed using the Perceived Availability of Social Support scale[17]. It is an 8-item measure that assesses the participant's perception of the social support systems that are available to them. Examples of questions include "Would someone be available to talk to you if you were upset, nervous, or depressed?" "Is there someone you could turn to if you needed to borrow M10...?" and "Is there someone you could turn to if you needed advice to help make a decision?".

Intimate partner violence will be assessed using the WHO's scale for emotional, physical, and sexual violence. Each item is measured on a 5-point Likert scale, ranging from 0 ("never") to 4 (very often). The emotional violence subscale has 7 items and the physical/sexual violence subscale has 9 items. Participants are asked to report on violence victimization and perpetration over the past 12 months[18].

4.3 Follow-up household visits

The aim is that the CCW visits each household on a bio-annually basis (I.e., every 3-9 months) throughout the duration of the study. During each follow-up visit, the enumeration will be updated (to enroll new household members and register deaths or migration of household members). Further, the medical condition of participants who were previously diagnosed for a chronic condition will be reassessed, medical diagnosis and drug treatment will be updated, BP measurement and risk-based DM screening will be repeated.

The entire study procedure will be captured in the eHealth application specifically developed for ComBaCaL, which will support the CCWs in implementing the study procedures correctly. A summary of the study procedures and variables collected are compiled in the table below:

Time (months)	***0 day***	***+3 months***	***+6 months***	***Every 3 to 9 months***
	Baseline visit	*1st follow-up visit*	*2nd follow-up visit*	*Further follow-up visits*
Oral and written information	+			
Verbal Household consent	+			
Enumeration	+			
Individual written consent	+			
Medical history	+			
Current medication	+			
Participant Characteristics	+			
BP measurement	+			+
DM screening	+			
Mental health and psychosocial assessment	+		+	+
Follow-up of participants with diagnosed chronic condition		+	+	+

4.4 Feasibility and acceptability assessment

The above-described regular cohort study procedures will be conducted in conjunction with mixed-methods assessments to evaluate the feasibility and quality of their implementation. All stakeholders, including CCWs, cohort participants, supervising health care professionals and researchers involved in this pilot study may be approached for semi-structured interviews and/or focus group discussions (FGDs). CCWs, cohort participants, and supervising health care professionals may be part of contextual inquiries to observe actual interactions in the field. Additionally, CCWs might be asked to fill out scheduled surveys (i.e., Likert scale-based questionnaires and free text questions) to assess their perception of their work and support by the eHealth app. The informed consent form for these qualitative interviews is attached to this submission and will be used throughout the entire pilot cohort period. Participation in interviews, FGDs, and contextual inquiries can be declined without being asked for justification and without implication on further study participation. A first qualitative assessment is outlined in the first nested study (11.1) including the first interview guide (12.3). Additional qualitative assessments that might be applied at a later stage will be submitted in a future amendment to the ethics committee.

4.5 Assessment of interventions for management of NCDs

As outlined in section 2, this ComBaCaL pilot cohort will inform the ComBaCaL main cohort on feasibility and acceptance of community-based interventions for NCDs. As such, CCW provided

interventions will be piloted in the ComBaCaL pilot cohort. To keep this protocol clear and well structured, piloted interventions are listed as nested studies under section 11.

4.6 Withdrawal and discontinuation

Participants can withdraw cohort consent at any time without being asked justification. After withdrawal of consent, contact information of the former participant will be deactivated in the app and the individual will not be approached again by the CCW. However, possibility to re-enter the pilot cohort at a later time via direct contact with the CCW will be offered. Anonymized data collected until the time of withdrawal will be included in the analysis.

5. STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan

The ComBaCaL pilot cohort will be recruited from ten villages in Butha-Buthe and Mokhotlong districts in Lesotho. We estimate the average number of inhabitants per village to be at least 100. Anticipating a high proportion of inhabitants consenting to participation based on our team's prior work in these communities, we expect the total number of participants to be at least 900.

Quantitative analysis of health outcomes is not the primary goal of the pilot cohort; thus, no sample size calculations were performed. The number of villages was chosen to provide meaningful feedback on implementation procedures for the ComBaCaL main cohort using reasonable resources.

The distribution of baseline characteristics such as demographics, NCD risk factors and BP will be presented using descriptive statistics. Continuous variables are presented as means and standard deviations. Categorical variables are presented as counts and percentages. Also, longitudinal measurements of BP or other variables within the cohort will be analyzed descriptively. However, as the primary objective of the ComBaCaL pilot cohort is formative work, qualitative assessment will be the focus of the analysis using thematic analysis. It emphasizes identifying, analyzing and interpreting patterns of meaning within qualitative data. Braun and Clarke's thematic analysis approach for developing themes from qualitative data shown in 12.2 will be applied[19].

5.2. Handling of missing data

Quality and completeness of data collection will be regularly checked by the PI. In case of missing or inconsistent data, the principal investigator will directly contact the responsible CCW. As the CCWs are consistently present in the study village, data can be amended continuously. Quantitative assessment of health outcome data is not the primary objective of the pilot cohort, thus incomplete data will not compromise the success of the study. However, causes for inadequate data collection will be assessed to identify weaknesses in the data collection process to avoid them in the ComBaCaL main cohort.

6. REGULATORY ASPECTS AND SAFETY

6.1. Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol and the Declaration of Helsinki[20] as well as other locally relevant regulation such as the National Health Research and Ethics Committee of Lesotho (NHREC). The project leader and the PI acknowledges their respective responsibilities.

6.2. Notification of safety and protective measures

The sponsor and the PI are promptly notified (within 72 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The ethics committee will be notified of these measures and of the circumstances necessitating them within 7 days after the project leader and/or the PI were notified.

6.3. Serious adverse events

Prescription and use of HTN and DM treatment will follow current international recommendations. All HTN and DM drugs used in Lesotho have a well-established safety profile.

Before start of the study, the study personnel will be trained on relevant treatment guidelines and potential adverse events (AEs) and serious adverse events (SAEs) of HTN and DM drugs. In case of SAEs, the CCW must inform the PI within 72 hours of his/her awareness of the SAE. SAEs are defined as following: a) life-threatening event, b) hospitalization, c) persistent or significant disability or incapacity, d) congenital anomaly / birth defect, e) death. The PI must then inform the Sponsor within 72 h and the local ethics committee in Lesotho within a month.

6.4. Amendments

Besides analysis of health data and mixed-method assessments of study implementation procedures, we plan to conduct several non-randomized community-based health interventions in the pilot cohort population. All interventions deviating from here-described regular cohort follow-up procedures as well as other substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the ethics committee in separate amendments before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants and small changes regarding wording or language in the questionnaires.

6.5. End of project

Upon project completion or discontinuation of the study, the ethics committee is notified within 90 days. Upon termination of data analysis, all health-related data will be anonymized in the research data-base. However, as we strive for integration of the ComBaCaL project's service delivery and eHealth solution into the existing government health system, relevant health-related data of participants will be made available to local health care professionals that are directly involved in further care of participants during and after the study if agreed upon by the participants.

6.6. Compensation

Participation in this study is not anticipated to cause any substantial additional risk or cost to the participant. Therefore, we will not pay compensation to the participants.

7. FURTHER ASPECTS

7.1. Overall ethical considerations

We consider the risk of this pilot cohort for participants to be minimal. Participation is voluntary, and informed consent can be withdrawn at any time.
The evidence generated in this pilot cohort is intended to inform the ComBaCaL main cohort and thereby contributes to the quality of scientific evidence, generated in the ComBaCaL main cohort that aims at informing future national and international clinical guidelines to improve NCD care in low-resource settings. Additionally, the community-based activities of the ComBaCaL project provide the added benefit of building a healthy and friendly community environment through

community advocacy and participation, and helping to raise awareness and knowledge of NCDs within villages in Lesotho. Participants will benefit from improved NCD service in their villages through presence of trained eHealth supported CCWs. Thus, the ComBaCaL project is likely to have a direct positive impact on health outcomes of participants as well as generating evidence to improve context-specific NCD care delivery on a longer perspective.

7.2. Risk-Benefit Assessment

There is no substantial health risk associated with study participation. The NCD screening, diagnosis and management during the study do not differ from guideline 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.
Data collection will entail questionnaires, automated BP measurements, urine dip-stick and capillary blood sugar and HbA1C measurements if indicated. None of the study components has the potential to cause significant harm to participants. Highest priority will be given to protection of health-data privacy. No personalized data will be shared with people other than directly involved study team members.
Participants of the ComBaCaL pilot cohort will benefit from access to guideline-conform active community NCD screening, diagnosis and management support. The NCD eHealth app provides algorithms for screening and diagnosis of sub-clinical DM and HTN and the CCW will do rapid testing for RBG, FBG, HbA1C and BP measurement available to cohort participants who might otherwise not have access to these services. This will likely improve early case detection and thus enable access to potentially life-saving treatment. Additionally, close follow-up in the community by trained eHealth-supported CCWs is likely to improve NCD care for participants compared to standard clinic-based care. Thus, besides its scientific value for the improvement of context-specific NCD service delivery, the study activities also have a high potential to positively influence the health outcome of participants.

7.3. Rationale for the inclusion of vulnerable participants

All consenting inhabitants of the chosen pilot cohort villages will be enrolled into the pilot cohort. Many NCD risk factors such as overweight or unhealthy diet affect adults and children alike and are often transmitted from one generation to the next within families. To assess the prevalence of NCD risk factors in the whole population and to understand their evolution throughout childhood, adolescence and adulthood, we will enrol children of all ages into the cohort. As for all other participants, the enrolment of children into the cohort only entails observational data collection.

8. QUALITY CONTROL AND DATA PROTECTION

8.1. Data recording and quality measures

All survey data collected in the villages will be directly entered using a dedicated tablet-based eHealth application with regular synchronization to a safe server. The use of a direct entry technology (rather than copying paper-based source data onto another platform) reduces errors. We will ensure that the CCWs have adequate supplies and materials so that data collection and transportation of materials (e.g., finger-prick needles, urine dip-sticks etc.) will be assured at any time.

The data will be monitored regularly by the PI in Lesotho with additional data quality checks from monitoring and quality team in Lesotho with close collaboration with a data-manager in Switzerland. Participant records will be checked for accuracy and consistency. Any aberrant response or unjustified missing data will be identified. These queries will be taken to the CCWs and any data errors corrected. Furthermore, the PI will visit field activities on a regular basis and provide direct supervision to ensure accuracy of data entry in the field. All staff will be trained according to study specific procedures.

For quality assurance the ethics committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

8.2. Confidentiality and coding

The study team as well as the CCWs are bound to strict medical confidentiality. The CCWs will be particularly trained on the matter of confidentiality and data security.
Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the pilot cohort health data bases and other project specific documents, participants are only identified by a unique participant number. A separate file linking personal data of participants to the unique participant numbers allowing for identification of participants and linkage to individual health data will be created. This file will be stored separately on the computer and only be accessible by the PI, Sponsor/chief-investigator, project manager or study physician. If medically indicated, the PI will make relevant parts of this file available to stakeholders relying on identifiable data for research or disease management such as local healthcare professionals. Thus, each local health care professional will only be given access to identifiable health data of the study participants within the pilot cohort village he or she is responsible for.

9. FUNDING / PUBLICATION / DECLARATION OF INTEREST

This research project is funded by the Swiss Development Cooperation, through a grant issued to SolidarMed and the World Diabetes Federation through a grant issued to SolidarMed. Findings of the ComBaCaL pilot cohort will be shared at relevant stakeholder meetings in Lesotho as well as at national and international scientific conferences. Relevant findings will be published in peer-reviewed journals, preference will be given to journal with an open-access publication model. 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.

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11. NESTED STUDIES:

Various nested studies will be implemented as part of the ComBaCaL pilot cohort over time to assess the different phases of the cohort appropriately.

11.1. Nested study: Cohort inception phase and NCD treatment initiation

Nested study Title	eHealth-supported NCD cohort establishment and community-based NCD treatment initiation performed by lay health providers in rural villages in Lesotho: A mixed-method study nested in the ComBaCaL pilot cohort
Background and Rationale	In Lesotho, many healthcare service delivery options focus on HIV/TB, care for NCDs is often neglected. A community-based approach will help to increase early diagnosis, early treatment initiation and systematic patient management. Further, it may build a healthy and friendly community environment through community advocacy and participation, and help to raise awareness and knowledge of NCDs in the community. The ComBaCaL pilot cohort aims to inform the design and implementation of the subsequent ComBaCaL main cohort. This nested study aims to assess in different observational mixed-method approaches the implementation procedures of the pilot cohort such as training and supervision of CCWs, functioning and usability of the eHealth application, different NCDs dispensing and treatment initiation models by the CCWs, acceptability of CCWs, and perception of local health care professionals, participants and CCWs about the piloted NCDs care model.
Objective(s)	This nested mixed-method observational intervention study will assess three major procedures to inform the main cohort: 1) the inception phase of the ComBaCaL pilot cohort, i.e. the selection and training of CCWs, cohorting of all study areas, deploying the eHealth app, etc. 2) different NCD treatment initiation models for BP and DM, after diagnosis in the community (see details below under procedures) 3) usability of the eHealth app and effect on CCWs and their work
Outcome(s)	This study will have quantitative and qualitative outcomes to assess the two objectives. Quantitative (descriptive): 1) Time and costs required to select, recruit, train and equip the CCWs 2) Time in days required by the CCWs to cohort their entire village-cluster

	3) Number and characteristics of individuals enumerated, refusing cohort consent and enrolled into the pilot cohort 4) Proportion of participants tested for HTN and DM. 5) Proportion of participants newly identified living with HTN and DM. 6) Proportion of newly diagnosed participants with HTN or DM successfully initiated on treatment 7) Proportion of participants that disengaged from care until the end of the study 8) Number of CCWs interactions with health care workers at the facility or study personnel. 9) Number of times the CCWs interactions of the eHealth application 10) Usage of eHealth app including performance related data (e.g., number of visits and tasks performed per CCW) Qualitative (narrative): 1) CCWs satisfaction with the eHealth application and its specific features (e.g., perceived empowerment when using eHealth app) 2) Evaluation of the eHealth application in terms of technical functionality in the field (offline-online sync), user design, incorporated medical algorithms, etc. 3) Acceptability and satisfaction with the CCWs involvement by the participants and the health care workers at the health facilities 4) Patient preferences about the level of decentralization of NCD care and task-shifting form healthcare professionals to CCWs 5) Recruitment, selection and training process of new CCWs 6) Health professionals' perception about the community NCDs care
Study Design	Mixed-method approach (qualitative & quantitative measures) • Observational Part: For cohort inception procedures • Interventional Part: Open-label for treatment initiation • Qualitative Part Nested within ComBaCaL pilot cohort
Inclusion/Exclusion Criteria	For the quantitative part, all cohort participants are eligible. However, as NCD screening will only be offered to adults aged above 18 years, no minors will be offered the study-specific procedures (see next chapter) of this nested study. For the qualitative part, we will purposively select from five groups of participants: a) CCWs b) Health care workers at corresponding facilities and district health authorities c) Participants newly identified with DM or HTN and thereafter not linking to initiation d) Participants newly identified with DM or HTN and thereafter linking to initiation e) Community members screened for both DM and HTN and screened negative f) Other important stakeholders that are part of ComBaCaL (study staff, MoH, etc.)
Procedures	The CCWs will be equipped with a personal tablet installed with the eHealth application, and other equipment's that are described in detail in the pilot cohort (see recruitment 3.2.1). Patient care and communication is coordinated through the app.

The NCD eHealth app is protected by a password, only known to the PI and the CCWs. The NCD eHealth app serves as a data collection tool and as a patient management tool to keep track of the medication prescribed to each participant. The app will keep overview of all due dates (next refill date, follow up dates, POC results) and automatically alert the CCWs for an action.

Management of HTN

HTN and DM screening and diagnosis are described in the pilot cohort procedures described above.

To assess different NCDs dispensing and treatment initiation models by the CCWs, there will be two different interventions in the 10 pilot villages:

A) In five "community-based initiation villages"

In case of confirmed HTN, the participants will be initiated on hydrochlorothiazide (HCTZ) by the CCW in the community.
patients will be started on 25 mg HCTZ once daily. After drug initiation, the CCW will visit the patient regularly. In case of any perceived side-effect, the CCW will consult the supervising healthcare professional at the health facility or the patient will be referred to the facility depending on patient preference. Treatment target is a systolic BP of 140 mmHg or lower. If after one month, the treatment target is not met, the dose of HCTZ will be increased to 50 mg once daily. If after another month, the treatment target is still not met, the patient will be referred to the health facility.

Before prescription, the CCW will inform the patient about possible side-effects of the medication and perform a urine dip-stick. Only asymptomatic patients without significant proteinuria (defined as 3 or more on a scale of 5) will start drug treatment in the village without previous consultation at the health facility. Patients with history of renal disease, current significant proteinuria or any of the above-mentioned clinical alarm symptoms or patients refusing drug treatment by the CCW will be referred to the health facility.

B) In five "facility-based initiation villages"

Patients with confirmed HTN will be referred to the closest health facility for initiation of antihypertensive treatment independent of their medical history, current symptoms or preferences. In two of the five control villages, the patients will be sent to the health facility alone, while in the three other villages, the CCW will offer to accompany the patients to the health facility and attend the consultation together with the patient if desired.

Management of DM

All patients with a FBG of 5.6 mmol/l or higher will receive a diabetes life-style counselling by the CCW including information about the disease, associated risks and treatment possibilities. Patients will be advised to restrict calorie intake if BMI is above 25, to be physically active, to avoid snacks between regular meals, to eat food with high fibre content, to stop smoking and to refrain from excessive alcohol consumption. During the initial phase of life-style intervention, the CCW will visit the patients regularly to check adherence to life-style changes and to repeat weight measurements. After one month, the CCW will repeat an FBG

measurement. The POC of care HbA1C at the baseline will be done and 3 to 6 months.

A. In five "community-based initiation villages"

Patients with confirmed DM will be initiated with metformin by the CCW.

Patients will be started on 500mg metformin and 20mg atorvastatin once daily. After initiation of drug treatment, the CCW will visit the patient weekly. In case of any perceived side effect, the CCW will consult the supervising healthcare professional at the health facility and PI or the patient will be referred to the facility depending on patient preference. If no side effects occur, metformin will be increased in steps of 500mg daily every week until the maximum dose of 2g per day is reached. After two weeks on the maximum dose, FBG will be repeated. If FBG is above 10mmol/, patients will be referred to the health facility.

Before prescription of medication, the CCW will inform the patient about possible side-effects of the medication and perform a urine dip-stick. Only asymptomatic patients without proteinuria will start drug treatment in the village without previous consultation at the health facility. Patients with history of renal or liver disease, current significant proteinuria or any of the above-mentioned clinical alarm symptoms or patients refusing drug treatment by the CCW will be referred to the health facility.

B. In five "facility-based initiation villages"

Patients with an RBG of 11 mmol/l or higher or with an FBG of 7 to 9.9 after one month of life-style intervention will be referred to the closest health facility for initiation of drug treatment. In two of the five control villages, the patients will be sent to the health facility alone, while in the three other control villages, the CCW will offer to accompany the patients to the health facility and attend the consultation together with the patient if desired.

Management of DM and HTN combined

If a participant is diagnosed with HTN and DM concomitantly, the same procedures apply as in case of isolated disease except for the change of BP target from 140mmHg systolic to 130 mmHg. Interventions for HTN and DM can be combined in one visit, thus the number of visits for patients with comorbidity of both diseases should not be higher than for patients with isolated disease. Same as patients with either DM or HTN can have combined visit.

Refill in the community via LHW

Participants will get their drug refills at the CCW place if they prefer, otherwise, participants can collect them at their nearest health facility. The CCWs will keep DM and HTN drugs at their place for the patients to refill. The CCWs will get their stock from their nearest health facility. This will help to minimise the movement to the health participants with stable conditions.

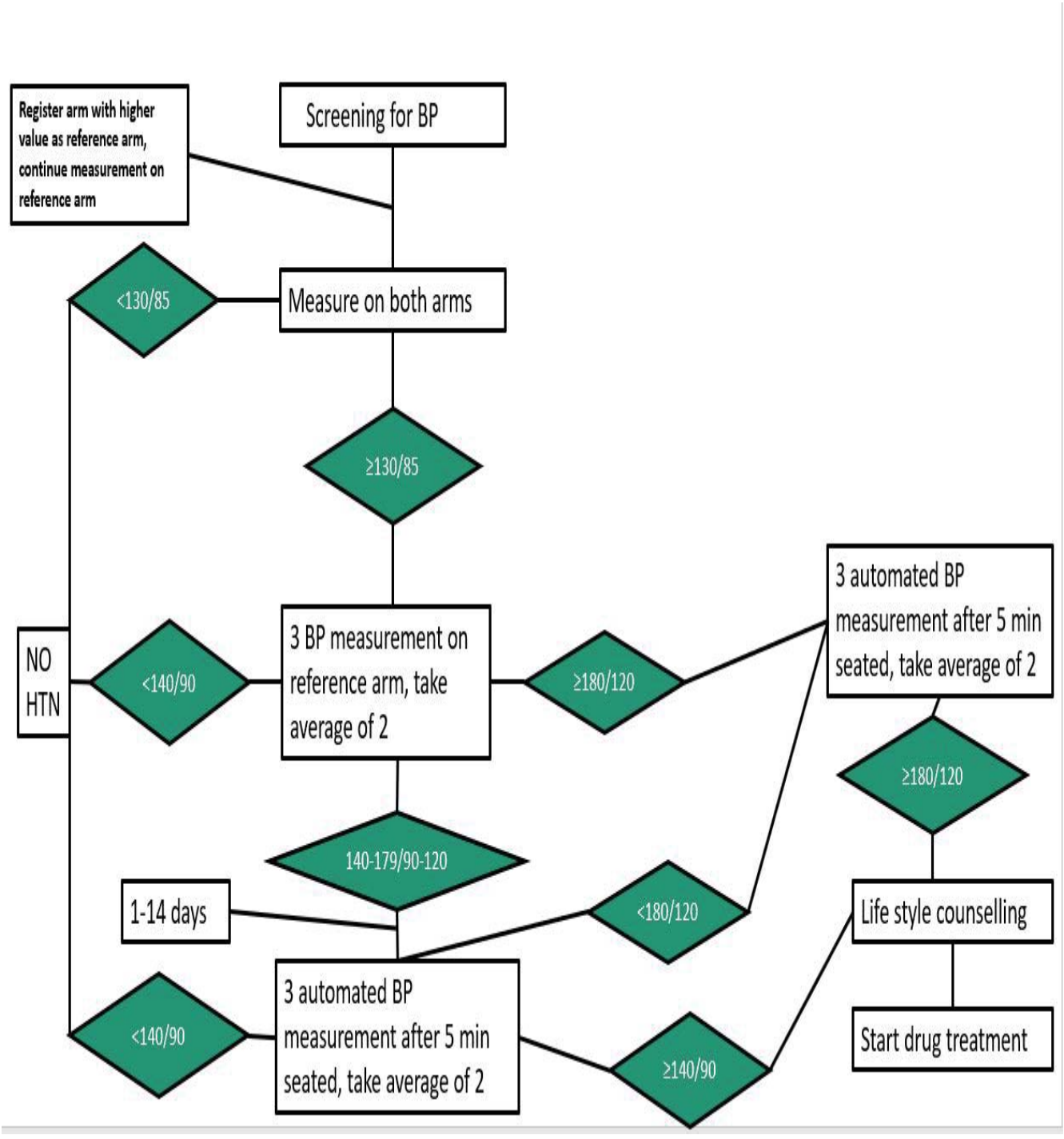
Qualitative research

We will explore perception and the acceptability of NCDs eHealth App, recruitment of CCWs and the Community- based NCD care in
a) Focus Group Discussions (FGD) with health care workers from the health facilities which piloting villages fall under.

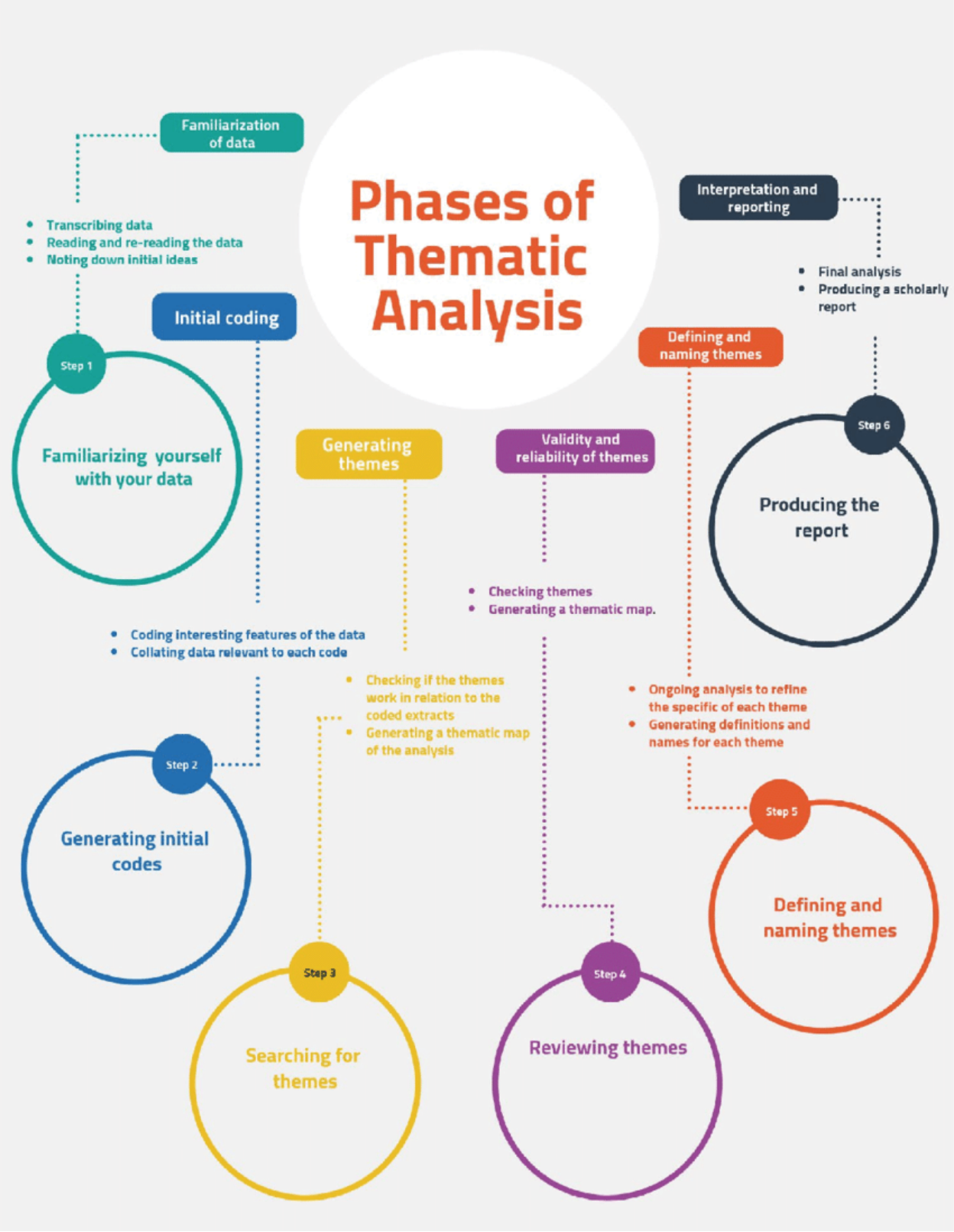
	b) Individual interviews CCWs and participants from pilot villages c) Regular survey administered through eHealth app to capture actual perception of usability by CCWs d) other key stakeholders as appropriate
Measurements	Quantitative outcomes will be measured continuously using a) data directly the eHealth application, b) data from the corresponding health facilities and c) data from study logs that document the study implementation procedures d) subjective data of the CCWs while using the eHealth app Qualitative outcomes will be assessed among the above-mentioned conducting focus-group discussion (FGD), observations in the field, and individual in-depth interviews (IDI). FGDs will only be conducted for health care workers. We plan at least one FGD per district among health care workers. All other qualitative data will be collected during IDIs. Data will be collected by trained facilitators using piloted interview questionnaires and guides, in the local language (Sesotho).
Sample Size	The quantitative outcomes are purely descriptive; thus, no target sample size was determined. The qualitative outcomes are based on purposive sampling and will last until saturation is reached.
Statistical Considerations and Analyses	Quantitative: Appropriate descriptive statistics Qualitative: Recordings from the audio recorder will be translated to English and then transcribed verbatim. Data analysis will be performed inductively and deductively, following the main steps of qualitative data analysis and will be performed as an iterative process for each objective: a) reviewing the transcripts, b) summarizing content, c) identifying codes and themes, d) developing a codebook, d) systematically applying the codebook to all transcripts, e) compile the main themes, f) summarize the main findings
Ethical considerations	The risk of this pilot study and the nested study to participants is minimal. Participation is entirely voluntary, and informed consent can be withdrawn at any time. The evidence generated in this ComBaCaL pilot cohort is intended to inform the ComBaCaL main cohort and thereby future national and international clinical guidelines and helping to raise awareness and knowledge of NCDs within villages in Lesotho.
Study Duration	**Open cohort**
Study Schedule	February 2022: First-Participant-In (planned)

12. APPENDICE

12.1: Algorithm for HTN screening



12.2: An illustration of Braun and Clarke's thematic analysis approach for developing themes from qualitative data



12.3 The interview guides and questions for qualitative

We refer to attached documents called:

The interview guides_v1_13122021

12.4 Informed Consent Forms

We refer to attached documents, called:

Informed Consent ComBaCaL Pilot Cohort_V1_English_13122021
Informed Consent ComBaCaL Pilot Cohort_V1_Sesotho_13122021
ComBaCaL Pilot Cohort Study-Qualitative sub-study_v1_Lesotho_English_13122021
ComBaCaL Pilot Cohort Study-Qualitative sub-study_v1_Lesotho_Sesotho_13122021

12.5 Mental Health Assessment tools

We refer to attached documents, called:

GHQ Measure
PAS Measure
WHO 2006_IPV Measure_all
WHODAS 2.0_12itemsINTERVIEW

12.6 Staff List

We refer to attached document called:
Investigator CV_ComBaCaL Cohort Pilot