An integrated intervention for chronic care management in rural Nepal: a type 2 hybrid effectiveness-implementation study

CURRENT STATUS: ACCEPTED

Trials BMC

Dan Schwarz
Nyaya Health Nepal

dan@possiblehealth.org*Corresponding Author*
ORCiD: https://orcid.org/0000-0002-6975-4519

Santosh Dhungana
Hurley Medical Center

Anirudh Kumar
NYU Langone Health

Bibhav Acharya
University of California San Francisco

Pawan Agrawal
Nyaya Health Nepal

Anu Aryal
Nyaya Health Nepal

Aaron Baum
Icahn School of Medicine at Mount Sinai

Nandini Choudhury
Nyaya Health Nepal

David Citrin
Nyaya Health Nepal

Binod Dangal
Nyaya Health Nepal

Meghnath Dhimal
Nepal Health Research Council

Bikash Gauchan
Nyaya Health Nepal

Tula Gupta
Nyaya Health Nepal

Scott Halliday
Nyaya Health Nepal

Biraj Karmacharya
Dhulikhel Hospital

Sandeep Kishore
Icahn School of Medicine at Mount Sinai

Bhagawan Koirala
Tribhuvan University Institute of Medicine

Uday Kshatriya
Nyaya Health Nepal

Erica Levine
Icahn School of Medicine at Mount Sinai

Sheela Maru
Nyaya Health Nepal

Pragya Rimal
Nyaya Health Nepal

Sabitri Sapkota
Nyaya Health Nepal

Ryan Schwarz
Nyaya Health Nepal

Archana Shrestha
Kathmandu University School of Medical Sciences

Aradhana Thapa
Nyaya Health Nepal

Duncan Maru
Nyaya Health Nepal

DOI:
10.21203/rs.2.15845/v2
SUBJECT AREAS
Integrative & Complementary Medicine
KEYWORDS
noncommunicable diseases, chronic disease, non-physician healthcare workers, community health workers, clinical decision support systems, motivational interviewing, Nepal

Abstract

Background In Nepal, the burden of non-communicable, chronic diseases is rapidly rising, and disproportionately affecting low- and middle-income countries. Integrated interventions are essential in strengthening primary care systems and addressing the burden of multiple comorbidities. A growing body of literature supports the involvement of frontline providers, namely mid-level practitioners and community health workers, in chronic care management. Important operational questions remain, however, around the digital, training, and supervisory structures to support the implementation of effective, affordable, and equitable chronic care management programs. Methods A twelve-month, population-level, type 2 hybrid effectiveness-implementation study will be conducted in rural Nepal to evaluate an integrated non-communicable disease care management intervention within Nepal's new municipal governance structure. The intervention will leverage the government's planned roll-out of the World Health Organization's Package of Essential Non-communicable disease interventions (WHO-PEN) program in four municipalities in Nepal, with a study population of 80,000. The intervention will leverage both the WHO-PEN and its cardiovascular disease specific technical guidelines, HEARTS, and include three evidence-based components: 1) non-communicable disease care provision using mid-level practitioners and community health workers; 2) digital clinical decision support tools to ensure delivery of evidence-based care; and 3) training and digitally-supported supervision of mid-level practitioners to provide motivational interviewing for modifiable risk factor optimization, with a focus on medication adherence, and tobacco and alcohol use. The study will evaluate effectiveness using a pre-post design with stepped implementation. The primary outcomes will be disease-specific, "at-goal" metrics of chronic care management; secondary outcomes will include alcohol and tobacco consumption levels. Discussion This is the first population-level, hybrid effectiveness-implementation study of an integrated chronic care management intervention in Nepal. As low- and middle-income countries plan for the Sustainable Development Goals and universal health coverage, the results of this pragmatic study will offer insights into policy and programmatic design for non-communicable disease care management in the future.

Background

The burden of non-communicable diseases (NCDs) is rising globally,[1, 2] and four major NCD classes – cardiovascular disease, chronic respiratory disease, diabetes, and cancer — contribute to more deaths globally than all other diseases combined, with enormous health and economic implications currently and in the future.[3, 4] This is especially true in low- and middle-income countries (LMICs), where governments are struggling to plan for the increasing health and financial implications of these pandemics.[5] As governments strive to achieve the Sustainable Development Goals[6] and work towards universal health coverage,[7] the rising NCD pandemic poses significant barriers to these aspirations.

In spite of this growing need for long-term chronic disease care, LMIC healthcare systems are not well-equipped to address this disease burden.[8] Historically focused on delivering acute, episodic care, these healthcare systems lack the capacity to provide on-going longitudinal care for patients with diseases best managed across a lifetime. This is especially true for patients with multiple chronic conditions, who often struggle to receive care for co-morbid diseases without numerous, fragmented encounters.[9] Health workforce shortages, and an emphasis on physician-provided care, have contributed to significant access, coverage, and quality deficits.[10, 11]

There is a growing body of evidence that chronic diseases in LMICs can be well-managed, especially at the primary care level, by mid-level practitioners (MLPs).[10, 12-21] MLPs offer a feasible, affordable, and high-quality alternative to traditionally physician-delivered care. This can help to circumvent access barriers, thereby leading to fewer late-stage presentations and complications of otherwise manageable chronic conditions.[20] Evidence suggests the quality of MLP-delivered care improved when they are well-managed, assigned clear scopes of work for which they are appropriately-trained, and receive supportive supervision[22-24] by senior clinicians with continual, improvement-focused feedback.[20]

Simultaneously, the role of community health workers (CHW) is increasingly recognized as an important augmentation to facility-based care delivery strategies, offering critical linkages, referrals, and coordination of care within communities.[25-27] The potential value of CHW-augmented chronic care management has only recently become of major interest.[12-18, 27-29] Global experience

suggests that the greatest benefits come from CHWs when they are accredited, well-managed, salaried, continually trained and supervised, integrated into strong primary care systems, and part of continual data feedback loops with facility-based providers.[25]

Taken together, the need and opportunity for LMIC healthcare systems – already struggling with workforce shortages – to build strong chronic care programs managed by MLPs and augmented with CHWs is compelling. However, there is a paucity of large-scale implementation data available to evaluate such models of care delivery, making it difficult for LMIC policy-makers to decide whether to adopt these strategies.

In response to the growing need for evidence-based NCD service delivery, the World Health Organization has compiled a set of protocols within the Package of Essential Non-Communicable Disease Interventions for Primary Health Care in Low-Resource Settings (WHO-PEN). [30, 31] These protocols constitute simple decision-making algorithms for the screening, diagnosis, and management of major NCDs, helping to ensure quality care provision in primary care settings, especially in areas already struggling with workforce shortages.

The WHO, together with the World Heart Federation, the World Stroke Organization, the United States Centers for Disease Control, the International Society of Hypertension, and the World Hypertension League, has released complementary guidelines to the WHO-PEN, called HEARTS.[32] The acronym stands for: **H**ealthy lifestyle; **E**vidence-based treatment protocols; **A**ccess to essential medicines and technology; **R**isk-based management; **T**eam care and task-sharing; and **S**ystems for monitoring. In addition to bringing specific guidelines for cardiovascular disease management into the technical base of WHO-PEN, these guidelines provide expanded details around health information systems, workforce development and training, and service delivery. As such, they augment the systems focus of WHO-PEN in incorporating NCD care into broader healthcare systems strengthening.

Recent evidence has shown the feasibility of adopting WHO-PEN at the primary care level in LMICs, including implementation with MLPs.[33-36] These data suggest that it is feasible for to deploy WHO-PEN at the population level in primary care settings. While WHO-PEN and HEARTS do not focus explicitly on the engagement of CHWs in these care delivery chains, there is a strong potential for

augmenting MLP-based WHO-PEN and HEARTS care at facilities with CHW-based strategies in the community.

Clinical decision support (CDS) tools facilitate the use of algorithmic care protocols such as WHO-PEN by health workers at the point of care. HEARTS provides specific CDS algorithms for cardiovascular conditions. These algorithmic CDS tools are used globally, across high-income and LMIC settings, in a range of conditions, including heart disease and diabetes.[37-42] CDS tools are essential both for managing individual conditions as well as structuring the comprehensive care of patients with multiple comorbidities. In addition to CDS tools integrated into electronic health records (EHRs), there is a growing body of evidence to support mobile-phone based CDS tools, often targeted at MLPs[43] and CHWs.[44] These CDS tools are especially well-equipped for clinical situations in which clear algorithms exist, such as the WHO-PEN and HEARTS protocols.

Historically, in many LMICs, there has been scant emphasis placed on risk factor reduction through lifestyle modification for NCD prevention or to reduce risk factors for the progression of these diseases when already diagnosed. While many of the contributing etiologies for NCD epidemics are far upstream of individuals' lives, and out of their control,[45] there are certain risk factors that are modifiable by patients, families, and health workers. Among others, it is widely documented that alcohol and tobacco consumption directly contribute to the development and progression of cardiovascular disease, diabetes, and chronic obstructive pulmonary disease (COPD).[46] These risk factors have been marked as priority targets for NCD control moving forward, including in both the WHO-PEN and HEARTS protocols.[8, 47]

WHO-PEN Protocol #2 (and republished in HEARTS), "*Health Education and Counseling on Healthy Behaviors*," describes risk factor modification.[31] However, while emphasizing health education, there is often very little guidance provided to health workers for meaningful engagement with patients and communities to accomplish these difficult lifestyle modification goals. There are many limitations to purely knowledge-focused approach health education, verses one that emphasizes self-efficacy and patients' own values.[48]

Motivational interviewing (MI), originally validated in substance-abuse interventions, approaches

behavior change through a style characterized by empathy and collaboration aimed towards the patient's readiness for change.[49] Trial data demonstrate the efficacy of MI for behavior change such as smoking and alcohol cessation.[50-55] These data raise the possibility of MI program development, led by MLPs within LMICs, as a viable strategy for improving risk factor modification interventions, and specifically, as an augmentation to WHO-PEN, to strengthen its impact. Since many communities struggle with a lack of healthy nutritional options, dietary improvements are often difficult to realize. Reducing alcohol and tobacco consumption, however, are realistic options for risk factor modification interventions in even the poorest communities worldwide. Recent WHO-PEN guidance on "brief interventions" for alcohol and tobacco, in concert with MI-related interventions, offer practical options for addressing these challenges in the primary care setting.[48]

In Nepal, the burden of NCDs is rapidly growing,[56-58] within the context of an overburdened healthcare system.[12, 58, 59] Nepal's government is committed to achieving the Sustainable Development Goals and universal healthcare, and has a specific focus on expanding health services for NCDs. In addition to recently enshrining the right to healthcare into its Constitution,[60] Nepal's government has committed to addressing the NCD epidemic by launching a Multisectoral Action Plan in 2014[61] and establishing the Nepal Non-communicable Disease & Injury Poverty Commission in 2016.[58] Furthermore, the Ministry of Health and Population has committed to a step-wise national implementation of PEN.[58, 59, 62] Nonetheless, the way forward will be challenging, and innovative strategies are clearly needed to accomplish these ambitious goals.[58]

Nepal has an extensive history of both MLP and CHW interventions.[63-65] Recent evidence from within the country has demonstrated the potential for CHWs to be involved in hypertension management.[66] Many communities rely on MLPs for primary care,[43, 67] and there has been some experience with MLPs using CDS tools for algorithmic care provision.[43] However, to date there are no large-scale implementation data of integrated, MLP- and CHW-based NCD care management at the population level. Similarly, while there has been some anecdotal description of MI being utilized in urban areas for select populations, there is no population-level data surrounding the use of MI for NCD risk modification. As the country endeavors to develop cross-sectoral strategies to address the

growing NCD epidemic, these staffing models, coupled with CDS tools and MI-based adherence and risk modification, are important policy and programmatic considerations.

We will conduct a type 2 hybrid effectiveness-implementation trial (where effectiveness and implementation are simultaneously tested with equal priority simultaneously)[68, 69] to evaluate an integrated NCD care management intervention. The intervention will leverage the Nepali government's planned roll-out of WHO-PEN in two rural districts. In addition to the government's roll-out, the intervention will include three evidence-based components: 1) NCD care provision by MLPs and CHWs that is integrated between facilities and communities; 2) CDS tools for MLPs and CHWs to optimize adherence to best practices; and 3) training and supervision of MLPs in using MI to facilitate tobacco and alcohol cessation.

Methods

Study aims

As above, we will conduct a type 2 hybrid effectiveness-implementation trial to evaluate an integrated NCD care management intervention in rural Nepal. The intervention is described in depth in the Supplementary File 1.

Study implementers

Healthcare workers and research staff from the non-profit organization *Nyaya Health Nepal*, their collaborators in the Ministry of Health and Population and Nepal Health Research Council, and collaborating researchers form the study team will lead the study. *Nyaya Health Nepal* has been working in a public-private partnership with the Ministry of Health and Population for over ten years in rural Nepal to deliver community- and facility-based health services, and this study will leverage this pre-existing partnership and care delivery network. *Nyaya Health Nepal* operates with a United States-based non-profit organization, *Possible,* to advance national and global healthcare systems policy and practice priorities.

Study setting

The study will take place in Achham and Dolakha districts of Nepal across four municipalities. Following recent healthcare decentralization, Nepal's 750 municipalities manage primary healthcare

delivery. The intervention will be implemented in a step-wise fashion in coordination with municipal-level government authorities and study staff.

Achham is a remote, impoverished district of 260,000 people, with large migrant populations and a history of social disruption during the Nepali civil conflict.[70-74] Achham has one of the highest district-level under-five mortality rates[75] and one of the lowest human development indices in the country.[76] The study implementers have been delivering some NCD-related care at the district-level Bayalpata Hospital and to communities within the hospital's catchment population since 2008. Bayalpata Hospital serves approximately 90,000 outpatient and 3,000 inpatient visits per year. CHW services include proactive case detection, care coordination, and counseling. The study will include a catchment population of approximately 50,000 in Achham across two municipalities.

The second district is Dolakha, one of the hardest hit districts in the 2015 earthquakes.[77] *Nyaya Health Nepal*'s work in Dolakha is based at Charikot Primary Health Care Center, which serves approximately 60,000 outpatients per year, with similar CHW services to those in Achham's. The study will include a population of approximately 30,000 in Dolakha across two municipalities. Thus, the total expected study population will be 80,000.

Within the context of the public private partnership between the government and *Nyaya Health Nepal*, no user fees are charged for any facility-based or community-based services, in either Achham or Dolakha, thereby mitigating financial access barriers to care delivery and study participation.

Within the study setting, MLPs for the NCD intervention are locally defined as the Nepali cadre of Health Assistants, who have three years of post-secondary medical training. The CHWs in this intervention have secondary-school-level education, and are fully employed, with on-going supervision by Community Health Nurses (CHNs). They receive initial training of approximately one month when they are hired, and on-going weekly trainings to continually improve their skillsets. The CHWs are employed by the public-private partnership between *Nyaya Health Nepal* and the Ministry of Health and Population. They are distinct from the robust Female Community Health Volunteer network that exists throughout Nepal,[63, 78] who have historically focused on vaccination, public health messaging, and other community preventive interventions rather than on household care

delivery and follow-up. These staffing, supervision and training structures are described in greater detail in the Supplemental File 1 and 2.

Study populations

For primary quantitative outcomes, the study population will include adult patients (≥18 years of age) who qualify for a diagnosis of hypertension, type II diabetes, and/or COPD, according to WHO-PEN guidelines, and are engaged in longitudinal care by *Nyaya Health Nepal'*s team in Achham and Dolakha. The study will limit enrollment to the catchment areas served by both the facility-level and CHW-level services deployed by *Nyaya Health Nepal.* Study participants will be initially enrolled during facility-based visits at Bayalpata Hospital and Charikot Primary Health Care Center prior to the completion of intervention roll-out, and are considered engaged in longitudinal care if they have at least one follow-up hospital visit after 12 months of their initial visit. Digital health records that link between the facility-based EHR and the CHWs' mobile-phone applications will be utilized to share patient data across settings, when available. CHWs can identify potential patients in the community and refer them to the facility for diagnosis confirmation, following which they could be included in the study. Patients' receipt of care will not be contingent upon their enrollment in the study; all patients will continue to receive care per routine service delivery. This represents an exhaustive convenience sampling method as all eligible patients identified at Bayalpata Hospital and Charikot Primary Health Care Center may be enrolled in the study. Exclusion criteria are (1) individuals planning to migrate from the study area prior to twelve months of exposure to the intervention, or (2) individuals explicitly requesting exclusion from the study or declining to consent (see Supplemental File 3) for the study. For implementation components, staff members, patients, community leaders, and government officials will be approached for key informant interviews (KIIs) and focus group discussions (FGDs), as described below.

Study design

This is a prospective, mixed-methods type 2 hybrid effectiveness-implementation study to evaluate an integrated NCD care management intervention. We plan to apply both qualitative and quantitative methods in a complementary manner,[79] in order to meaningfully assess both patient-level and

population-level outcomes and the effectiveness of the implementation strategy. We will study the intervention's impact on patients' disease management outcomes after 12 months of being enrolled in NCD care using a pre-post design across both sites.

1) We will study the implementation of the intervention utilizing both quantitative and qualitative methods applying the RE-AIM (Reach, Efficacy, Adoption, Implementation, and Maintenance) framework [80].

Data collection is developed and integrated within the routine course of delivering care, which is an ethical, acceptable, and affordable approach in this setting. See Figure 1 for a trial flowchart and Supplemental File 4 for a SPIRIT research reporting checklist. is not feasible nor ethically acceptable to obtain data on a comparison (control) group in this population. Given the lack of national or local NCD systems, no data are available from other sources prior to the start of the study.

Study outcomes

The study has two Specific Aims: effectiveness (Specific Aim 1) and implementation (Specific Aim 2), as detailed in Table 1. For Specific Aim 1, the primary outcome will be the proportion of patients who meet disease-specific, evidence-based control measures at the completion of their initial twelve months engaged in treatment. These "at-goal" metrics aim to serve as simplified measures to assess disease control status, recognizing the limitations associated with multiple disease-specific metrics in settings like rural Nepal, especially for patients with multiple co-morbid conditions. These are presented in Table 2.

Table 1: Metrics for Specific Aim 1 (efficacy) and Specific Aim 2 (implementation)

Aim	Outcome/ RE-AIM Element	Indicator	Definition
Specific Aim 1: Efficacy	Primary outcome: control of NCD conditions	Condition-specific "at goal" metrics	-% of enrolled NCD patients achieving "at goal" 2), at the completion of the study period
	Secondary outcome 1: tobacco use	Tobacco use status	-% of enrolled NCD patients who were using tol enrollment who are non-users or who have red their tobacco intake, at the completion of the s
	Secondary outcome 2: alcohol use	Alcohol use status	-% of enrolled NCD patients who were alcohol c enrollment who are non-drinkers or who have r >50% alcohol intake, at the completion of the s
Specific Aim 2: Implementation	Reach	Home visit coverage	-% of enrolled NCD patients having a CHW hom measured monthly
		Clinic visit coverage	-% of enrolled NCD patients having an MLP visi measured monthly according to the patients in seen that month based on protocol-based guid
		Demographic, geographic barriers and facilitators	-% of enrolled NCD patients whose CHW has GI their households, describing barriers/facilitators individuals' access, and identifying contributors

		variation/inequities
	Loss to follow-up	-% of patients, stratified by demographic data a conditions, that are lost-to-follow-up after enrol
	Monthly patient touch-points	-Number of monthly per-patient touch-points, i interactions by both MLPs and CHWs
Efficacy	Evidence-based hypertension management	-% of enrolled hypertension patients in accorda evidence-based recommendations, as prescribe algorithms, assessed quarterly by EHR audits
	Evidence-based diabetes management	-% of enrolled diabetes patients in accordance based recommendations, as prescribed by clini assessed quarterly by EHR audits
	Evidence-based COPD management	-% of enrolled COPD patients in accordance wit based recommendations, as prescribed by clini assessed quarterly by EHR audits
Adoption	Village cluster adoption	-% intended village clusters receiving intervent
	Timely adoption	-% intended village clusters rolling-out interver months of schedule, according to local governa to roll-out the intervention
	CHW adoption	-% CHWs trained in intervention implementatio six months -% of trained CHWs retained in their positions a completion of the study period
	MLP adoption	-% MLPs trained in intervention implementation -% of trained MLPs retained in their positions at completion of the study period
Implementation	Care integration	-% of all NCD patients enrolled at the facilities s at home within first month
	CHW supervision model	-% scheduled CHW supervision field visits comp stratified by CHN and district, measured quarte -% of scheduled quarterly data review meeting CHWs and CHNs, measured quarterly
	CHW home visit fidelity	-% of enrolled NCD patients with 100% of algor home visits received -% of topics included at each session as dictate condition-specific algorithms, assessed during t supervision field visits by CHNs, measured qua
	Referrals	-% of patients appropriately referred to MLP ca by the clinical algorithms, assessed during the supervision field visits by CHNs, measured qua -% of patients referred by CHWs seen by MLPs prescribed time window according to the clinica (e.g. 24hours, 72 hours, 1 week), measured qu
	MLP supervision model	-% of enrolled NCD patients appropriately refer physician by MLPs as indicated by the clinical a assessed during monthly physician supervision measured quarterly
	MLP visit fidelity	-% of enrolled NCD patients with 100% of algor facility visits received, assessed during monthly supervision sessions, measured quarterly -% of diagnostic, treatment, and counseling top each session as dictated by the condition-speci assessed during monthly physician supervision measured quarterly
	Implementation challenges	-Exploratory and hypothesis-generating as reve FGDs and KIIs with CHWs, CHNs, MLPs, physicia and other relevant community stakeholders
Maintenance	Total intervention cost	-Cost of each intervention component and total the Joint Learning Network costing methodolog
	Intervention initiation costs	-%breakdown of initial (one-time) costs for inte (training, equipment, etc)
	Intervention maintenance costs	-% breakdown of maintenance (recurring) costs training, personnel, materials, and other)
	Facility vs. community costs	-% of costs of health care divided between faci community level
	Geographic cost variation	-Characterization of variance in costs between and districts within the intervention catchment
	Out-of-pocket patient costs	-% costs of health care divided between facility community level
	Integrated intervention cost-effectiveness analysis	-Pre/post intervention marginal effectiveness fo outcomes
	Cost per unit	-Intervention cost per enrolled patient -Intervention cost per capita -Projected cost to scale intervention nationally,

Table 2: Clinical definitions of “at-goal” status for each intervention condition

Non-communicable disease	Management metric	“At-goal” definition
Type II diabetes mellitus	Hemoglobin A1c OR fasting blood sugar	Hemoglobin A1c < 7.5 OR fasting b <130 mg/dL*
Hypertension	Blood pressure	Blood pressure <130/80mm Hg or tailored goal per risk stratification^
Chronic obstructive pulmonary disease	Exacerbation status	≤1/3 Anthonisen criteria ¥

Footnotes:

*Type II diabetes mellitus:

The 2018 American Diabetes Association guidelines [81] call for a goal A1c <7% for most patients or A1c<8% in "patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin." For our intervention, we established 7.5% as our goal to pragmatically accommodate both populations.

^Hypertension:

Based on the 2017 American College of Cardiology and American Heart Association guidelines,[82] we established <130/80mm Hg as a default goal, with patient-tailored goals for select patients (≥65 years of age, multiple co-morbidities, limited life expectancy, clinical judgement, patient preference).

¥Chronic obstructive pulmonary disease:

The 2017 update to the GOLD guidelines [83] define COPD exacerbation as an "acute worsening of respiratory symptoms that results in additional therapy." We used the Anthonisen criteria of worsening sputum volume, sputum purulence, and increased dyspnea to define the “worsening of respiratory symptoms” specified in the GOLD guidelines. We established a threshold of no more than one Anthonisen criterion as a pragmatic tool for determining clinical status.

Secondary outcomes for Specific Aim 1 will include the following. We will assess the individual “at goal” rates per condition. We will assess the persistence of the intervention for the subset of patients for whom we have the data (i.e., those enrolled within 12 months of the start of the study) on their 24 months’ outcome. Additionally, we will examine the tobacco and alcohol status of enrolled patients, specifically focusing on the proportion of patients who were tobacco users and/or alcohol drinkers at the time of enrollment, who have stopped all tobacco and / or alcohol intake, or reduced their intake by >50%, by the completion of the study period (Table 1).

For Specific Aim 2, the RE-AIM framework will be utilized to assess the implementation of the study intervention, with RE-AIM metrics as listed in Table 1.

Sampling strategy and power calculations

We will use exhaustive convenience sampling to screen all eligible patients seen across two facilities over a twelve month period into the analysis cohort. Based on historical formative data of patient volume seen at these two facilities, and accounting for an expected 30% attrition rate, we conservatively expect that at least 1000 patients will be eligible for enrollment into the cohort.

With this conservative number of 1000 as our expected sample size based on this convenience sampling, we conducted power calculations to determine the statistical power to detect a change in the “at goal” status. We calculate power based on a simplified design to compare paired proportions using a two-sided McNemar’s test with an 0.05 Type I error (alpha) level. The primary outcome is the proportion of patients who achieve their NCD control target (“at goal status”) after 12 months of being engaged in care. We used SAS version 9.4 (Cary, NC) to estimate power to detect a 5% difference between discordant proportions, i.e. proportions of patients whose “at goal” status changed from “not at goal” at baseline to “at goal” at follow-up, and vice-versa, in multiple scenarios where the total proportion of discordant patients ranged from 10% to 40% of all patients. Based on these assumptions, our power to detect a 5% difference in the discordant pairs is 69%, when the total discordant proportion is 40%, and the power is 99% when 10% of all patients were discordant.

Data collection

Quantitative data

Quantitative data for patient outcomes will be extracted from the facility-based EHR and the CHW's mobile phone application (Supplemental File 5), and will be used to assess Specific Aims 1 and 2. (Table 1) All implementation-related data for evaluating the performance of MLPs and CHWs (Table 1) will be collected by the responsible MLP and CHW supervisors in digitized checklists within the EHR and mobile phone application. Access to protected health information will be controlled and defined by user access groups according to clinician status. Data to be analyzed will be extracted via secure data queries from the EHR system in aggregate, partially de-identified form with external researchers signing a data sharing and use agreement prior to analysis. Cleaned, de-identified datasets will be made publicly available via a data repository.

Costing data for the intervention will be collected utilizing a "top-down" method, as described by the Joint Learning Network[84]. This method will document direct and indirect costs associated with the NCD care delivery intervention described here and related administrative functions (including planning and administration; training; supervision and monitoring and evaluation; data management; and continuous surveillance) will be disaggregated. Full methodology of direct and indirect costs is provided by the Joint Learning Network[84], and will be utilized for this study. For the purposes of this pragmatic study, this methodology will be appropriate to estimate the additional marginal costs of the intervention (rather than cost-savings or secondary cost implications) as compared to general standard of care.

Qualitative data

Qualitative data will be used for Specific Aim 2. (Table 2) Staff members, patients, community leaders, and government officials will be approached for KIIs and FGDs. Purposive sampling will be used, aiming to maximize heterogeneity across sex, socioeconomic position, healthcare issues, geographic location, age, caste-class, and other attributes. For each group, five key informant interviews will be conducted at each time point, as described below. One focus group discussion per group will be conducted at each time point.

KII and FGD guides will be developed in advance, and will vary across the study period, exploring

specific topics of concern. A locally validated, seven-domain framework of healthcare delivery analysis will be used to inform data collection.[85] These seven domains include health service operations, supply chains, equipment, personnel, outreach, societal factors, and structural factors. Qualitative data collection will focus on these areas to assess the implementation of the intervention. FGDs and KIIs will occur prior to the initiation of the intervention, and in intervals of six months throughout the study period, to assess on-going implementation status. All sessions will be conducted in Nepali. All qualitative data will be stored on a Research Electronic Data Capture (REDCap) database.[86] REDCap user access will be defined so that researchers only have access to de-identified study data. Any paper copies of data forms will be stored in locked cabinets inside locked rooms at district facilities. Once all data are fully transcribed and validated for quality, all paper copies will be destroyed. REDCap data will be deleted twelve months after the completion of the study period.

Data analysis

Analysis for Specific Aim 1: effectiveness

In order to assess the effectiveness of the intervention, as described above, the primary outcome will utilize disease-specific “at goal” metrics for each of the three study diseases: hypertension, type II diabetes, and COPD. We hypothesize that the integrated intervention will lead to a 10% increase in the “at goal” status of the combined disease cohorts, over a twelve-month follow up period.

We will use conditional multivariable logistic regression to assess patient outcomes at 12 months follow up, adjusting for potential confounding and/or effect modification by patients’ demographics (including age, sex, caste), municipality, district, mean distance to the hospital, and engagement in care (defined as number of facility-based and community-based encounters). We additionally hypothesize a 10% improvement in the status of each of the two secondary outcomes: tobacco and alcohol use, as measured by patient-reported outcomes in Table 1.

As a secondary analysis for Specific Aim 1, namely the time-varying nature of the outcomes, we will assess the longitudinal effect of the intervention, as measured in three-monthly intervals, throughout the study period, compared to baseline statistics at the time of each village-cluster enrollment.

Variables will be considered as either nominal or continuous (linear effect) predictors, and the generalized linear model framework will be used to estimate effect of time-varying repeated measure intervention implementation over the several steps of the wedged design. Differential impact from time of intervention will be evaluated with test of month × intervention interaction. Models will be fit using generalized estimating equations, e.g., using SAS Proc Genmod, to calculate valid standard errors in the presence of repeated measures over time and possibly correlated outcomes at the municipality level. Assumptions of over- or under-dispersion will be examined closely, and an estimated scale parameter or negative binomial models will be used as needed.

Analysis for Specific Aim 2: RE-AIM implementation framework

In this mixed-methods study, Specific Aim 2 will be assessed using the RE-AIM framework for implementation trials.[80] A full list of metrics, separated by each domain of the RE-AIM framework, is presented in Table 1. Additional details regarding the supervision and audit structure for MLPs and CHWs can be found in Supplemental File 1 and 2.

For the (M)aintenance of the intervention, we will assess the costs of the intervention, using the Joint Learning Network methodology[84]. Cost data will be analyzed and presented (Table 1) to help program planners and policy makers understand the implications for possible scale of a similar intervention by the government or other entity in the future.

For quantitative data within Specific Aim 2, a similar methodology of generalized estimating equations, as described above in the section on Specific Aim 1 analysis, will be applied. Data will be assessed in three-month intervals.

For qualitative data within Specific Aim 2, analysis will be on-going and iterative, so as to continually inform further qualitative data collection, focusing on timely and relevant implementation issues. Data from KIIs and FGDs will transcribed and coded using Grounded Theory Methodology.[87, 88] NVivo software will be used for qualitative data analysis.[89]

Discussion

Ethical approval and consent

This study has been approved by the Ethical Review Board of the Nepal Health Research Council

(#177/2018). Within the study, all patients will provide verbal informed consent to have their de-identified data analyzed and published. Care provision will be unrelated to consent, and there will be no difference in care provision based on consent status. Verbal informed consent will also be provided by all KII and FGD participants. No incentives will be provided to study participants, to avoid any conflict of interest or coercion to participate. Protocol modifications will be promptly communicated to the IRB and on the trial registry website by members of the research study team.

Safety considerations

There are minimal risks posed to patients, staff, or other key informants. The predominant risk is disclosure of protected health information, and/or qualitative data from KIIs or FGDs. All patient information will be stored on secure databases, and data access privileges will be heavily restricted. Unless otherwise deemed necessary for a specific analysis, all analyses will be conducted using a limited dataset. Qualitative data will be stored and protected as described above.

Data sharing

All deidentified data from this study will be made publicly available for other researchers to analyze at their discretion in the future, to further this field of research. Deidentified summaries of qualitative data will be made available as well.

Dissemination plan

Domestically within Nepal, six-monthly update meetings will be held between researchers and the Ministry of Health and Population to review on-going results. When completed, results of the study will be presented at the annual National Summit of Health and Population Scientists, organized by the Nepal Health Research Council, and at other relevant international conferences. Peer-reviewed publications will be drafted for international dissemination.

Trial Status

At the time of manuscript submission, the study is currently not yet recruiting participants. Participant enrolment is anticipated to commence beginning in February, 2020 is planned to continue for one year. Intervention deployment took place between July 2018 and will conclude in January 2020. This is study protocol version 1.2 and the version date is December 6, 2019.

Abbreviations

CDS = clinical decision support

CHN = community health nurse

CHW = community health worker

COPD = chronic obstructive pulmonary disease

EHR = electronic health record

FGD = focus group discussion

HEARTS = healthy-lifestyle counselling; evidence-based treatment protocols; access to essential medicines and technology; risk based charts; team-based care; systems for monitoring (WHO HEARTS Technical Package)

KII = key-informant interview

LMIC = low- and middle-income country

MI = motivational interviewing

MLP = mid-level practitioner

NCD = non-communicable disease

PEN = Package of Essential Noncommunicable disease interventions for primary care in low-resource settings (WHO PEN)

RE-AIM = Reach; Effectiveness; Adoption; Implementation; Maintenance

REDCap = Research Electronic Data Capture

WHO = World Health Organization

Declarations

Ethics approval and consent to participate:

This study has been approved by the Ethical Review Board of the Nepal Health Research Council

(#177/2018). Within the study, all patients will provide verbal informed consent to have their de-identified data analyzed and published. Care provision will be unrelated to consent, and there will be no difference in care provision based on consent status. Verbal informed consent will also be provided by all KII and FGD participants. No incentives will be provided to study participants, to avoid any conflict of interest or coercion to participate.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets supporting the conclusions of the study will be made publicly available in de-identified form upon conclusion of the study. The final trial dataset (in limited identifier format) will be accessible to researchers at the research performance site in Nepal—Nyaya Health Nepal—and co-investigators assisting with data analysis. Participating research institutions will enter into data sharing agreements (namely between the research performance site in Nepal—Nyaya Health Nepal—and any foreign institutions where investigators are assisting with data analysis) covering terms of access to specific limited datasets; provisions for storing, sharing, and using data; and methods for securing data transfer.

Competing interests:

PA, AA, DC, BD, BG, TG, UK, PR, SS, and AT are employed by and DS, BA, NC, SH, SM, RS, and DM work in partnership with a nonprofit healthcare company (*Nyaya Health Nepal,* with support from the US-based nonprofit, *Possible*) that delivers free healthcare in rural Nepal using funds from the Government of Nepal and other public, philanthropic, and private foundation sources. DS and RS are employed at an academic medical center (Brigham and Women’s Hospital) that receives public sector research funding, as well as revenue through private sector fee-for-service medical transactions and private foundation grants. DS and RS are faculty members at a private medical school (Harvard Medical School). DS is employed at an academic medical center (Beth Israel Deaconess Medical Center) that receives public sector research funding, as well as revenue through private sector fee-for-service medical transactions and private foundation grants. DS is employed at an academic

research center (Ariadne Labs) that is jointly supported by an academic medical center (Brigham and Women's Hospital) and a private university (Harvard T.H. Chan School of Public Health) via public sector research funding and private philanthropy. SD is a medical resident at a private academic medical center (Hurley Medical Center) that receives revenue through private sector fee-for-service medical transactions and a charitable private foundation. AK is a medical resident at a private academic medical center (NYU Langone Health) that receives public sector research funding, as well as revenue through private sector fee-for-service medical transactions and private foundation grants. BA is a faculty member at a public university (University of California, San Francisco). AA is a fellow supported by a public-sector research fellowship affiliated at and BKarmacharya and AS are faculty members at a private university (Kathmandu University). DC is a faculty member, SH is a graduate student at, and DC and SH are employed part-time at a public university (University of Washington). AB, DC, SK, SM, SS, and DM are faculty members at, and NC SH, and EL are employed by a private medical school (Icahn School of Medicine at Mount Sinai). MD is employed by the Government of Nepal (Ministry of Health and Population, Nepal Health Research Council). TG is a fellow with a bidirectional fellowship program (HEAL Initiative) that is affiliated with a public university (University of California, San Francisco) that receives funding from public, philanthropic, and private foundation sources. BKarmacharya is a faculty member at a public research university (Sun Yat-sen University). SK is the founding Executive Director at an advocacy and leadership network (Young Professionals Chronic Disease Network) that receives funding from individual philanthropy. SK serves as a consultant for Resolve To Save Lives on hypertension treatment and leads a partnership on multiple chronic conditions through his institution and Teva Pharmaceuticals. BKoirala is a faculty member at a public university (Tribhuvan University, Institute of Medicine). SM is a voting member on the Board of Directors with Group Care Global, a position for which she receives no compensation. RS is employed at an academic medical center (Massachusetts General Hospital) that receives public sector research funding, as well as revenue through private sector fee-for-service medical transactions and private foundation grants. AS is a faculty member at a private university (Yale School of Public Health). DM is a non-voting member on *Possible*'s Board of Directors, a position for which he receives no

compensation. All authors have read and understood Trial's policy on declaration of interests, and declare that we have no competing financial interests. The authors do, however, believe strongly that healthcare is a public good, not a private commodity.

Funding:

This trial was conducted with no external funding and was instead funded by Nyaya Health Nepal with financial support from the Government of Nepal, Possible, and other private and philanthropic support. The authors received no direct funding in support of this manuscript.

Author contributions:

Conceived the study: DS, SD, AK, NC, DC, SH, SK, RS, DM

Designed initial study protocol: DS, AK, NC, DC, SH, DM

Contributed to study protocol refinement: DS, SD, AK, BA, PA, AA, AB, NC, DC, BD, MD, BG, TG, SH, BKarmacharya, SK, BKoirala, UK, SM, PR, SS, RS, AS, AT, DM

Wrote the manuscript draft: DS, AK, NC, DM

Edited and revised manuscript draft: DS, SD, AK, BA, PA, AA, AB, NC, DC, BD, MD, BG, TG, SH, BKarmacharya, SK, BKoirala, UK, EL, SM, PR, SS, RS, AS, AT, DM

Reviewed and approved final manuscript draft: DS, SD, AK, BA, PA, AA, AB, NC, DC, BD, MD, BG, TG, SH, BKarmacharya, SK, BKoirala, UK, EL, SM, PR, SS, RS, AS, AT, DM

Acknowledgements:

We wish to express our appreciation to the Nepal Ministry of Health and Population for their continued efforts to improve the public sector healthcare system in rural Nepal. We also wish to acknowledge the deep contributions of the patients, health workers, and community members, for whom all this work is designed and aims to serve.

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Figures

	Cluster assignment	Intervention deployment	Enrolment	Trial start	Trial	Post-Trial
TIMEPOINT**	11/19	07/18-11/19	12/19 - onwards		12mo follow-up	
ENROLMENT:						
Cluster assignment	X					
Eligibility screen			X			
Informed consent			X			
INTERVENTIONS:						
[WHO PEN]		⟷			⟷	
[Care integration w/MLPs/CHWs]		⟷			⟷	
[Clinical decision support tools]		⟷			⟷	
[MI training + supervision]		⟷			⟷	
ASSESSMENTS:						
Efficacy measures				X	X	
Reach measures					X	X
Effectiveness measures					X	
Adoption measures					X	
Implementation measures					X	X
Maintenance measures						X

*Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration for examples from protocols.
**List specific timepoints in this row.

Figure 1

SPIRIT Figure

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