SCALE-UP OF PREVENTION AND MANAGEMENT OF ALCOHOL USE DISORDERS AND COMORBID DEPRESSION IN LATIN AMERICA

Deliverable 1 (D3.1)

SCALA Protocol

DEVIATIONS FROM ORIGINAL PROTOCOL

Moving from two-arm to four-arm design

The deviation is to move from a two-arm study to a four-arm study. In the original protocol, within each country, two municipal jurisdictions were investigator-selected, each with nine primary health care units (PHCU) as part of the study. In one municipal jurisdiction, the intervention municipality, the PHCU would receive both training and municipal support; in the other municipal jurisdiction, the comparator municipality, PHCU would continue practice as usual, with no training or municipal support. The hypothesis was that PHCU in the intervention municipality would measure the alcohol consumption of more patients and give advice to more heavy drinking patients than the PHCU in the comparator municipality.

In the revised protocol, the nine PHCU in the comparator municipality are randomly allocated to five PHCU receiving training (new Arm 2) and four PHCU continuing practice as usual (new Arm 1). The rationale for this approach is that it will enable us to test the independent impact of municipal support over and above just training. The hypothesis to be tested is that PHCU that receive both training and municipal support in the intervention municipality will measure the alcohol consumption of more patients and give advice to more heavy drinking patients than the PHCU who just receive training (Arm 2).

In addition, in the revised protocol, the nine PHCU in the intervention municipality are randomly allocated to four PHCU receiving a standard and longer clinical package and training (new Arm 4) and five PHCU receiving a shorter clinical package and training (new Arm 3), both new Arms 3 and 4 receiving municipal support. The hypothesis to be tested is that the PHCU that receive the standard and longer clinical package and training that is commonly implemented (new Arm 4) will not measure the alcohol consumption of more patients and not give advice to more heavy drinking patients than the PHCU that receive a shorter clinical package and training (new Arm 3). This will be tested over the first six months of the 18-month implementation period, and, if there is non-superiority of Arm 4 over Arm 3, Arm 4 will be collapsed into Arm 3 from month 8 onwards.

With the deviation, the study remains adequately powered to detect differences between Arm 3 and Arm 2, and between Arm 2 and Arm 1.

Cross-sectional patient self-complete questionnaire instead of prospective interview

The deviation is to move from patient follow-up interviews to cross-sectional patient self-completed questionnaires. In the original protocol, during month 3 of the 18-month implementation period, the first six consecutive screen-negative patients and the first six consecutive screen-positive patients identified by each PHCC were to be invited by the health care provider to give their written consent to complete two follow-up questionnaires, at six months and twelve months after the initial screening. In the revised protocol, at two time points, during the 18-month implementation period (months 3 and 15), on two separate days in each of month 3 and 15, providers will seek consent from the patient to self-complete additional questions in the waiting room before leaving the PHCU, handing the completed questions to a researcher in attendance. The rationale for the change is that, primarily due to the nature of catchment area of patients, it became apparent that it would be impossible to achieve sufficient follow-up rates required for valid analysis of data, with much too high a proportion of country-based resources used in order to try to achieve adequate follow-up rates.

Adjustment in primary outcome indicator

The deviation is to change the denominator for the main outcome variable from number of consulting adult patients in a given time period (e.g., one month) to number of registered adult patients. In the original protocol, the primary outcome was to be the proportion of consulting adult patients (aged

18+ years) intervened (screened and advice given to screen positives), calculated as the number of AUDIT-C positive patients that received oral advice or referral for advice to another provider in or outside the PHCC, divided by the total number of adult consultations of the participating providers per provider and per PHCC. In the revised protocol, the primary outcome will be the cumulative proportion of the number of adults (aged 18+ years) registered with the PHCU that have their alcohol consumption measured with AUDIT-C. The rationale is that the revised primary outcome is a measure of coverage, which is considered more intuitive and relevant for health systems change (similar to blood pressure - what proportion of patients have had their blood pressure measured). Due to this revision, there have been some adjustments to the definitions of some secondary outcomes.

Overall schedule adjustments
To take into account the changes in design, there have been some adjustments in the overall schedule.

Adjustment of measurement instruments
To take into account the changes in design, and, following tailoring and pilot testing, there have been some adjustments in the content of the measurement instruments.

INTRODUCTION

This protocol outlines the design of a quasi-experimental study to test the implementation of primary health care (PHC)-based programmes to measure, assess, advise and treat heavy drinking and comorbid depression at municipal level in three Latin American middle-income countries, Colombia, Mexico and Peru. Primary Health Care Units (PHCU) are the study participants, the units of allocation and analysis.

The three interventions (independent variables) for the PHCU are:

i. Intensity of clinical package and training (standard, versus short, versus none);
ii. Training of providers (present, versus absent); and,
iii. Community integration and support (municipal action present, versus absent).

The main outcome (dependent variable) is the proportion of the adult (aged 18+ years) population registered with the PHCU that has their alcohol consumption measured. Three hypotheses are to be tested:

Hypothesis 1: Municipal action leads to more sustainable coverage. After 18 months, the difference in coverage between municipal action present and municipal action absent is larger than after 12 months;
Hypothesis 2: The short clinical package and short training lead to higher coverage than no training; and,
Hypotheses 3: In the presence of municipal action, the short clinical package and short training do not lead to less coverage than the standard clinical package and standard training.

DESIGN

The study is a quasi-experimental design[1] , comparing changes in measurement and assessment for alcohol consumption and comorbid depression, and, if needed, advice and/or treatment between primary health care units (PHCUs) in intervention municipal areas and PHCUs in similar comparator municipal areas, with baseline activity, measured during a one-month period, as a covariate.

Intervention municipal areas are investigator-selected from Bogotá (Colombia), Mexico City (Mexico) and Lima (Peru). Comparator municipal areas are investigator-selected in Bogotá, Mexico City and Lima, on the basis of comparability with the intervention municipal area in terms of socio-economic and other characteristics which impact on drinking, health care and survival, comparable community mental health services, and sufficient geographical separation to minimize spill over effects from the intervention municipal area. Randomized selection of the municipal areas is excluded as the hypotheses and the study approach rely on municipal-level interventions. Municipal areas are chosen as a scalable implementation unit, given their jurisdictional responsibilities for prevention and health care services.

The units of allocation and analysis, study participants, are primary health care units (PHCUs) and the providers working in them. Within each PHCU, eligible providers include any fully trained medical practitioner, nurse or practice assistant with a non-temporary employment contract, working in the PHCU and involved in medical and/or preventive care. The providers sign an informed consent for their participation.

For the first six months of an 18-month implementation and test period, a four-arm design is adopted, Figure 1. Within each municipal area, PHCU are systematically invited to join the study, until nine PHCU

agree. Within the comparator municipal area, four PHCU are randomly allocated to control (Arm 1), and five PHCU to receive short training to implement a short clinical package (Arm 2). Within the intervention municipal area, in which all PHCU receive municipal action, five PHCU are randomly allocated to receive short training to implement a short clinical package (Arm 3), and four PHCU to receive standard training to implement a standard clinical package (Arm 4).

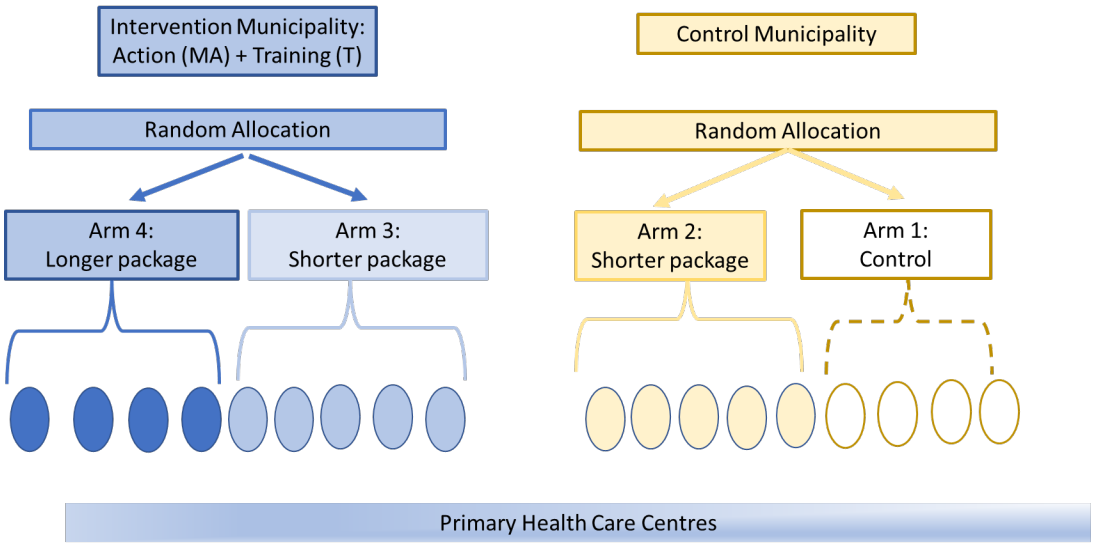

Figure 1. Study design for the first six months of the 18-month implementation period

By Month 6, non-superiority of Arm 4 (longer package with municipal action and training) over Arm 3 (short package with municipal action and training) will be tested. In the presence of clinical equivalence of a relative difference of cumulative coverage of patients whose alcohol consumption is measured of less than 10%, Arm 4 will be replaced by Arm 3 from month 8 onwards, Figure 2.

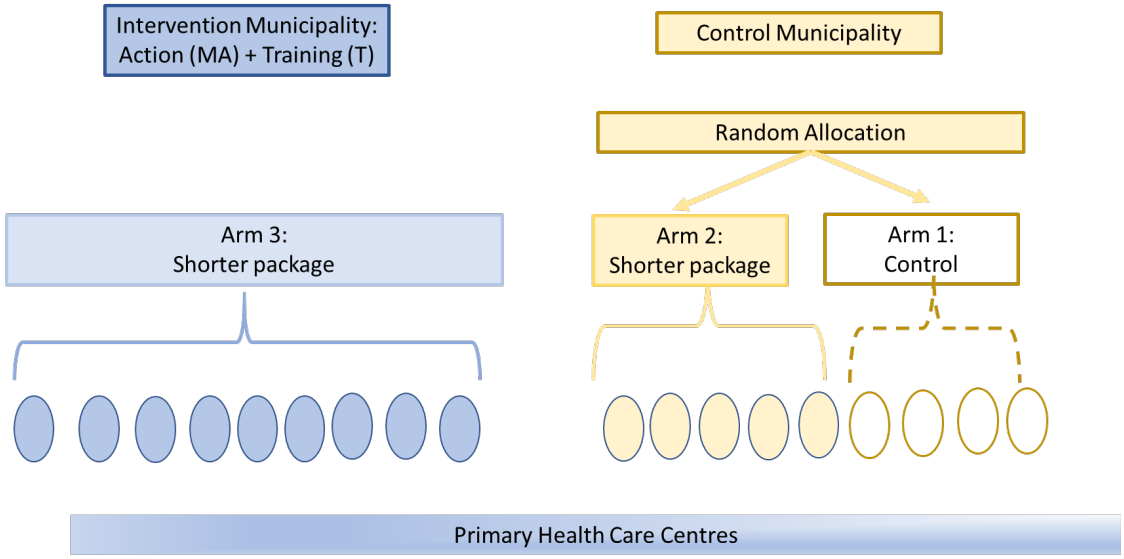

Figure 2. Study design from month 8 onwards, assuming no superiority of Arm 4 over Arm 3 during first six months of implementation.

The inputs to each of the four arms are summarized in Tables 1 and 2, and the standard and shorter clinical pathways that are implemented are summarized in Figures 3 and 4, and the overall timetable in Figure 5.

Table 1 Clinical Package and Training by Study Arm

	Standard package and training (Arm 4)	**Shorter package and training (Arms 2 and 3)**	**Control (Arm 1)**
Instruments	Short tally sheet: AUDIT-C[2] completed; if AUDIT-C ≥8, AUDIT-10[3] and PHQ2[4] completed; if PHQ2 ≥3, PHQ9[5] completed.	Very short tally sheet: AUDIT-C completed; if AUDIT-C ≥8, PHQ2 completed.	Very short tally sheet: AUDIT-C completed; if AUDIT-C ≥8, PHQ2 completed.
Provider material	Provider booklet on alcohol and depression: 43 pages plus 12-page 'quick guide'.	Provider booklet on alcohol and depression: 16 pages.	Provider booklet on alcohol and depression: 11 pages.
Patient advice and material for alcohol	Alcohol advice: 5-minute 10-step plan plus 10-page patient brief advice booklet.	Alcohol advice: 1-minute simple advice that the patient needs to drink less, plus 1-page patient brief advice leaflet.	Alcohol advice: 1-minute simple advice that the patient needs to drink less and provide a brief advice leaflet (if available).
	Patient alcohol leaflet: 1 page folded in half to give 4 sides.	Patient alcohol leaflet: 1 page folded in half to give 4 sides.	SCALA patient leaflet on alcohol not given. Provider booklet advises "If available, provide a leaflet on self-management of heavy drinking."
Patient advice and material for depression	PHQ9 score 10-14, provide patient leaflet on depression; PHQ 9 ≥14, use clinical judgement to consider if referral is required - if not provide patient leaflet on depression.	PHQ2 ≥3, patient leaflet on depression given.	SCALA patient leaflet on depression not given. Provider booklet advises "If available, provide a leaflet on self-management of depression and action to take if symptoms persist or worsen."
	Patient depression advice leaflet: 1 page, 3 columns.	Patient depression advice leaflet: 1 page, 3 columns.	Present practice.
Referral	Referral for very heavy drinking, depression, suicide risk: existing clinical judgement and practice.	Referral for very heavy drinking, depression, suicide risk: existing clinical judgement and practice.	Referral for very heavy drinking, depression, suicide risk: existing clinical judgement and practice.

Training	Training: two times two-hours training plus two times one-hour booster sessions (six hours total). Training will take place within the PHCU or clusters of PHCUs. Training will focus on practical skills in undertaking measurement and assessment, and in delivering brief advice, in using the questionnaires, and in knowing when and how to refer patients with more severe heavy drinking and moderately severe or severe depression to available services, such as community-based mental health and addiction centres. Training will, in addition, address attitudes, and perceived barriers and facilitators in implementing measurement and brief advice, contextualized to local circumstances.	Training: one two-hours training in PHCU, plus one-hour booster session (three hours total). Training will focus on practical skills in undertaking measurement and assessment, and in delivering brief advice for harmful alcohol use; instruction of 'care-as-usual' + leaflet for depression and severe cases requiring referral. Training will, in addition, address attitudes, and perceived barriers and facilitators in implementing measurement and brief advice, contextualized to local circumstances.	Present practice.
	Training for both the standard and shorter packages will be undertaken by members of the research team, accredited teachers, or addiction consultants, who will receive a full-day train-the-trainers session from a senior addiction specialist trainer. The training formats employed are didactic input, guided discussions, skills and practice modeled through videos and role plays. Training sessions are developed from[6-7].		

Table 2 Community Integration and Support by Study Arm

Intervention Municipal Area (Arms 3 and 4)	**Comparator Municipal Area (Arms 1 and 2)**
Community Advisory Board (CAB) of local stakeholders set up (including representatives of municipal area, PHCU, health services, non-governmental organizations, academia, media).	Present practice.
User Panel (UP) of local providers and patients set up.	Present practice.
CAB and UP review and tailor relevant materials of clinical package and training courses within the seven domains of: local and national guideline factors; individual health care provider factors; patient factors; interactions between different professional groups; incentives and resources; capacity for organizational change; and, social, political and legal factors[8-10].	Present practice.

CAB reviews barriers and facilitators and potential drivers of successful action[11-12].	Present practice.
CAB identifies potential adoption mechanisms and support systems[13], and reviews plans and components of community-based communication and media campaigns[14-16].	Present practice.
Integrator (champion and knowledge and practice broker) to serve as trusted and accountable leader[13]: facilitating agreement within the municipal area and health systems on shared goals and metrics; assessing and acting on relevant community resources; working at the systems level to make relevant practice changes for sustainability; gathering, analysing, monitoring, integrating, learning, and sharing data at the individual PHCU and city levels; identifying and connecting with system navigators who help PHCUs coordinate, access, and manage multiple services and supports; and developing a system of ongoing and intentional communication with PHCUs and cities.	Present practice.
Adoption mechanisms implemented[13], including: (i) demonstration of the superiority of the PHC package, its simplicity, and its alignment with the latest evidence of preventing and managing heavy drinking and of implementation science; (ii) engagement of identified leaders and building their capacity to lead and ensure broad adoption of the PHC package through guiding and supporting large-scale change; (iii) communicating the value of the PHC package to both municipal and PHC frontline staff; (iv) identifying and adjusting, as appropriate and possible, relevant policies at PHC and city levels to expedite the adoption of the PHC package, for example by adapting electronic health records; and, (v) identifying gaps in health system performance and the urgent need to prevent and manage heavy drinking to promote the needed will and energy to bring implementation of the PHC package to scale.	Present practice.
Support mechanisms implemented[13], including: (i) development of professional capacity for scale-up; (ii) development of infrastructure for scale-up, achieved through redesign rather than addition of new resources; (iii) linking to monitoring and evaluation, using reliable data collection and reporting systems that track and provide feedback on the performance of key processes and outcomes, for example monthly reporting on screening and brief advice activity; (iv) setting up learning systems to capture change ideas that are shown to result in improved performance assembling ideas into a change package. Knowledge should be shared between municipal actors and PHCUs through regular electronic newsletters and communications; and, (v) creating design factors that enhance sustainability including high reliability of the new processes, inspection systems to ensure desired results are being achieved, support for structural elements, and ongoing learning systems.	Present practice.
Communication and media campaign implemented[14-16], including (i) posters, leaflets and/or brochures placed at visible spots in the intervention municipality, e.g., in waiting rooms of PHCUs, health departments, banks; (ii) monthly newsletters (and other occasional emails) sent to the healthcare providers and other involved stakeholders in the intervention municipality, (iii) media presence through e.g. articles in local newspapers; interviews, reportages, promotion spots and/or media appearances on local radio, local TV and other local media, and (iv) workshops, forums and/or public local meetings for interested stakeholders such as healthcare providers, representatives of municipal health institutions and patients. All abovementioned activities will focus on reframing that it is heavy drinking that is the problem and that this can be helped to be reduced through primary health care-based measurement and advice programmes, addressing topics such as the harm of hazardous alcohol use in the general population, the (cost)effectiveness and importance of brief alcohol interventions and SCALA success stories.	Present practice.

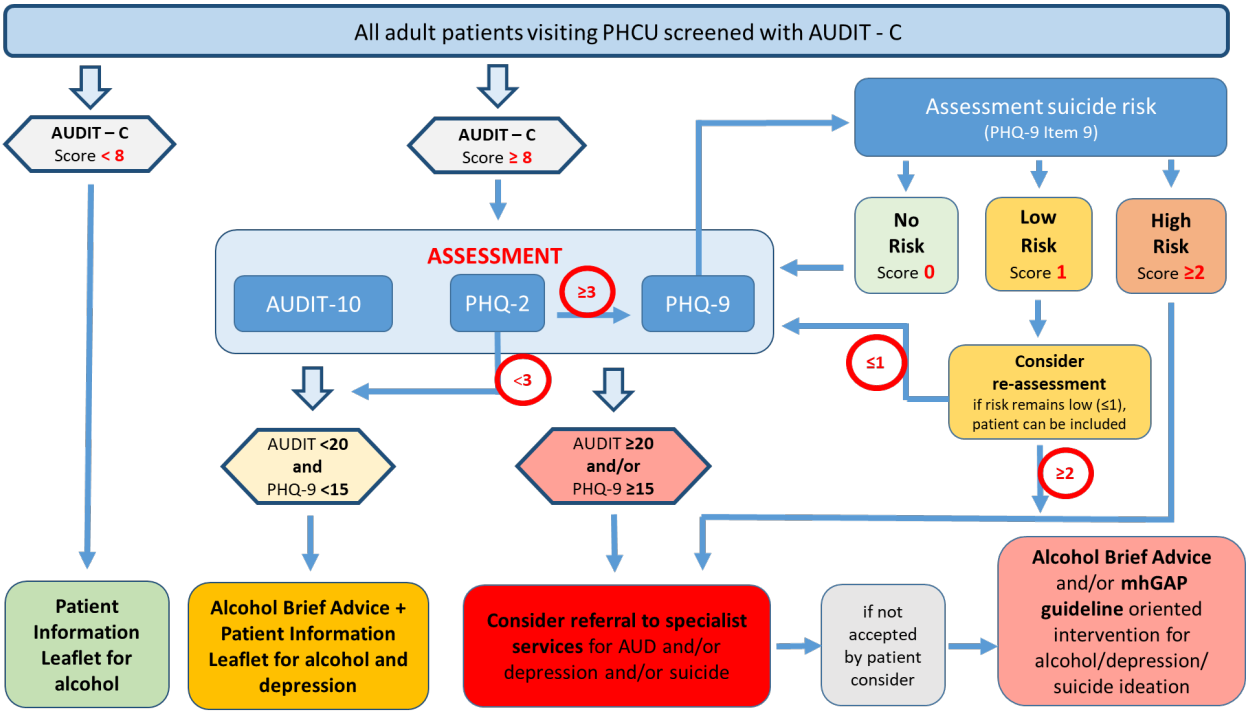

Figure 3. Standard Care Pathway for Arm 4 [mhGAP guideline[17]]

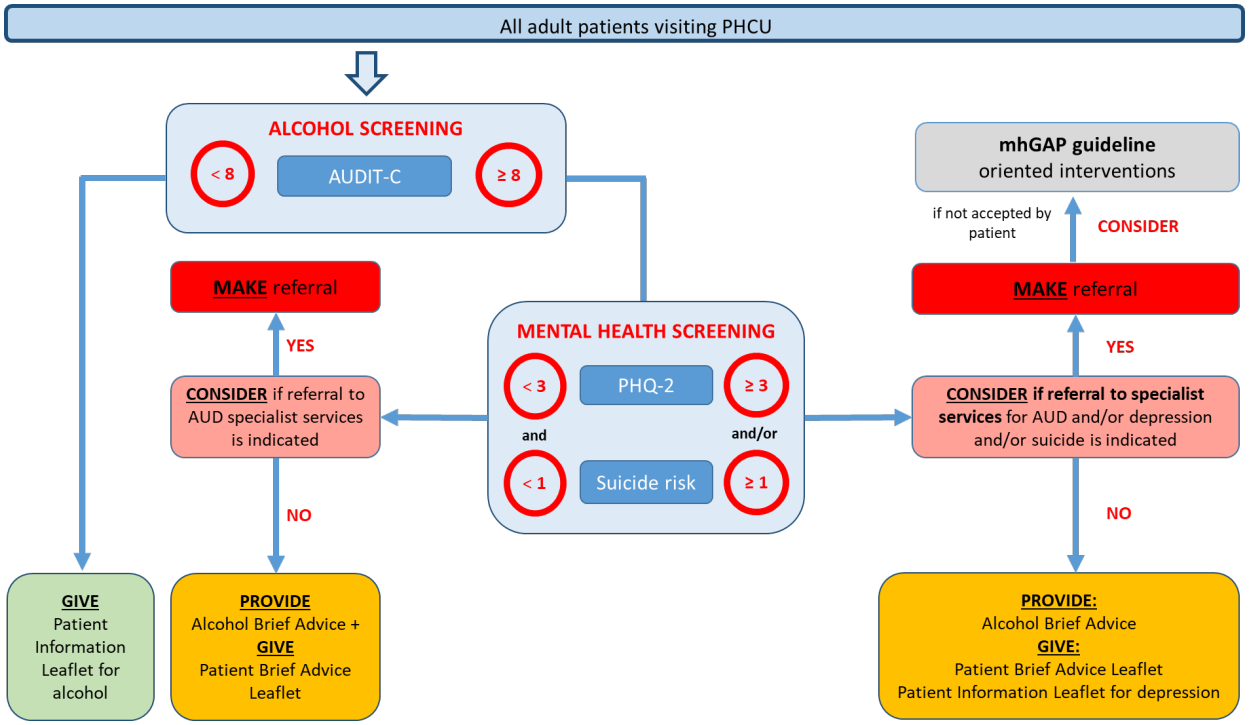

Figure 4. Short Care Pathway for Arms 1, 2, and 3 [mhGAP guideline[17]]

Figure 5 Timetable

Data collection and instruments

Municipal level information

At the level of the municipal area (or, when not available, at city, regional or country level), the following information will be collected from routinely available data at municipal, regional or country level:

- Geographical location in city;
- Demographic size of municipal area;
- Indicators of deprivation;
- Information on prevalence of alcohol consumption and related harm;
- Information on prevalence of depression;
- Description of current action to reduce alcohol-related harm;
- Jurisdictional responsibilities for health-related prevention and treatment;
- Structural relationships with primary health care services;
- Structural relationships with hospital-based services;
- Available data mapped to OECD better life initiative[18], including material living conditions (housing, income and jobs) and quality of life (community, education, environment, governance, health, life satisfaction, safety and work-life balance);
- Sustainable Governance Indicators[19], including the Status Index, which 'examines each state's reform needs in terms of the quality of democracy and performance in key policy fields', and the Management Index, focused on 'governance capacities in terms of steering capability and accountability'; and,
- World Values Survey data[20] for cross-cultural variation (Traditional vs. Secular-rational; and, Survival vs. Self-expression).

PHCU and provider level information

All contacted PHCU, including those who did and did not agree to be part of the study, will provide information on:

- Numbers of registered patients, divided into age 0-17 years and 18+ years; and,
- Numbers and professions of provider staff (including physicians, nurses, nurse technicians, midwifes, psychologists, social workers, and others).

At recruitment, PHC providers will provide data on their:

- Age;
- Gender;
- Profession (doctor, nurse, practice assistant etc.);
- Time worked in the PHC.

Provider-based measurement and assessment of alcohol consumption and comorbid depression and record of advice and treatment given (tally sheets)

Based on the validated methodology of the ODHIN project[7, 21], PHC providers will document activity by completing anonymous paper tally sheets that record eligible patients' (aged 18+ years) AUDIT-C scores[2], if administered, AUDIT-10[3], PHQ-2[4] and PHQ-9[5] scores, and the advice or treatment given to each patient. The tally sheets will record the age, sex, and educational level of the patient, the latter as a proxy measure of socio-economic status. Data will be collected for the one-month baseline measurement period, and for each calendar month of the 18-month implementation and test period. PHCUs will return data on the number of adult (aged 18+ years) consultations per provider for the one-month baseline measurement period, and for each of the 18 months of the implementation and

test period. Monthly data will be collected and reported with accumulation of coverage over time. Formal reporting will be undertaken at baseline, and for coverage achieved by month 12 and by month 18 of the 18-month implementation and test period. Tally sheets will include an identifying code of the provider, PHCU, country and study arm, but no identifying code of the patient. Data will be extracted and sent to the project's data warehouse at Technical University Dresden on a monthly basis.

Provider-based attitudes and experiences.

At recruitment, and at two time points during the 18-month implementation period (months 3 and 13), providers will provide data on their attitudes and experiences to working with patients with heavy drinking and comorbid depression, Table 3.

Table 3 Overview of the measures used in the provider questionnaire

Measure used	**Constructs measured**
Shortened Alcohol and Alcohol Problems Perception questionnaire[22]	Role security, therapeutic commitment
Abbreviated Maslach Burnout Inventory[23]	Emotional exhaustion, depersonalization, personal accomplishment
Utrecht Work Engagement Scale[24]	Work engagement
Alcohol knowledge[25]	Awareness of drinking guidelines, social norms regarding drinking
Perceived barriers questionnaire[26]	Perceived barriers
Opinion on screening (based on[27])	Pros and cons of screening, social norms of screening, intention to screen
Self-efficacy in delivering the SCALA protocol (based on[28])	Self-efficacy
Context assessment for community health (COACH) tool[29]	Resources, Community engagement, Monitoring services for action, Work culture, Leadership
Evaluation of SCALA community action[15]	Exposure to campaign/adoption mechanisms/support systems, perceptions of campaign/adoption mechanisms/support systems
Attributes of innovation questionnaire[30] - Only intervention group	Relative advantage, Compatibility, Complexity, Trialability and Observability
Experienced barriers (based on the driver diagram[12]) - Only intervention group	Experienced barriers

Providers will complete a short questionnaire after each of the training and booster sessions that they attended (before baseline assessment and at months 4 and 8). The questionnaires that are adapted based on specific training contents, will assess the participants' experience of the training, measuring satisfaction with the components of the training aspects, as well as their perceived utility . Two measures included in the main provider questionnaires, SAAPPQ and self-efficacy, will be included in order to assess the specific impact of the training, independent of the effect of the implementation of the intervention.

The specific content, number and timing of the training-related questionnaires will depend on the study arm: Arm 2 and 3 participants will fill in two questionnaires, one after training and one after the booster session; while Arm 4 participants will fill in four questionnaires, one after each of the two trainings and one after each of the two booster sessions.

Extended Tally Sheets

As part of quality control, in all four Arms at two time points, during the 18-month implementation and test period (months 3 and 15), and, if Arm 4 changes to Arm 3 in addition at month 9 only for Arm 4, providers will complete extended tally sheets on two separate days in each month. The extended tally sheets will include an identifying code of the provider but no identifying code of the patient. The extended tally sheet will include: additional information from the patient on alcohol knowledge[25], social norms[31] and alcohol health literacy[32] as it informs the content of advice given; and, additional information from the provider on contextual characteristics that informed their advice giving. The extended tally sheets will include a consent form for the patient and self-completed additional questions for the patient to complete, once the consultation has ended.

Self-completed additional questions by patient

On two separate days, during months 3 and 13, following the consultation with the extended tally sheet, patients who are literate will be invited to give consent to self-complete additional questions in the waiting room before leaving the PHCU, handing the completed questions to a researcher in attendance. No patient identifying information will be included in the patient questionnaires. Six domains, serving as quality control, will be included:

i. AUDIT-C;
ii. PHQ-2;
iii. Experiences of the consultation;
iv. Views on being asked about alcohol consumption;
v. Alcohol Health Literacy; and,
vi. Exposure to communication and media campaigns on alcohol.

On each day, 270 patient questionnaires will be collected across all PHCUs, with up to 1080 questionnaires completed in total across the four days.

Key informant interviews

A number of individual or group interviews will be undertaken throughout the project with key stakeholders – providers, user panel members, CAB members, project partners, and any other people involved in the implementation of the SCALA project. Depending on the stakeholder and their involvement in the project, the topics of the interviews will cover topics such as the necessary adaptation to the protocol; the experience of implementing the programme in primary health care practice; and the perception of the municipal support and the community campaigns, see Table 5 and accompanying text in the *Process Evaluation* section below.

Observations

The training sessions with the primary health care providers, and the meetings of the CABs will be observed by a neutral observer in order to take note of additional possible barriers in implementation of the protocol that emerge through the trainings and meetings. Participant responsiveness will also be observed, see Table 5 and accompanying text in the *Process Evaluation* section below.

Economic data for return-of-investment analyses

Within SCALA, we will conduct return-of-investment (RoI) analyses, by assessing for each dollar invested in scaling up delivery of screening and brief interventions in primary health care in Columbia, Mexico, and Peru, how many dollars will be saved by reductions in health care utilization. The return of investment will be defined as the [return on investment = (gain from investment – cost of

investment) / cost of investment]. For details on the data required for RoI analyses, see Table 4.

Table 4. Country-level collection of economic data for return-of-investment analyses

Costs of Investment		**Gains of investment**	
Cost unit	***Data source***	***Cost unit***	***Data Source***
Cost of providing training and booster sessions to PHCU staff	Time and materials required, documented by study team	Costs and utilization of *primary health care* (number of visits) by major disease categories	National statistics, ministry of health, local researchers, or other publications
Setting up and maintaining Community Advisory Boards and User Panels	Time and materials required, documented by study team	Costs and utilization of *accident and emergency* facilities (number of admissions) by major disease categories	National statistics, ministry of health, local researchers, or other publications
Direct costs for implementing the clinical pathway (routine measurement, further assessment, brief interventions, referral)	Staff salary and time required, documented by PHCU administration and providers	Costs and utilization of *inpatient* facilities (number of admissions, length of stay) by major disease categories	National statistics, ministry of health, local researchers, or other publications
Additional costs for implementing the clinical pathway	Documented by PHCU administration	Costs and utilization of *outpatient* facilities (number of admissions) by major disease categories	National statistics, ministry of health, local researchers, or other publications

For the RoI analyses, the effects of increased coverage of alcohol brief advice among primary health care patients will be modelled using effect sizes from previous meta-analyses[33]. To translate the reduced intake of alcohol into health gains, we will calculate alcohol-attributable fractions for major disease categories using the InterMAHP tool[34]. These fractions will then be applied to the cost data outlined in Table 4 to estimate the alcohol-attributable costs per disease category.

Process evaluation

As the intervention is embedded in a complex system involving actions and actors at different levels (individual, organisational, municipal), a thorough process evaluation will be carried out to complement and better understand the outcomes. Through the process evaluation, the implementation with its fidelity and adaptation will be assessed, along with the drivers of scale-up and contextual factors influencing the implementation, the drivers, and the outcomes. This will be achieved in four blocks: driver diagram creation; barriers and facilitators analysis; assessment of implementation, mechanisms of impact and context; and, further contextual and policy analysis.

Driver diagrams

Driver diagrams[12] will be used in order to describe the intervention and its causal assumptions, providing the theory of change through displaying what contributes to intervention aim and what are the relationships between primary drivers, secondary drivers and specific change ideas/activities. The initial general driver diagram, Figure 6, will be modified based on local contexts and adapted throughout the duration of the project in order to understand how scale up varies in the different cities.

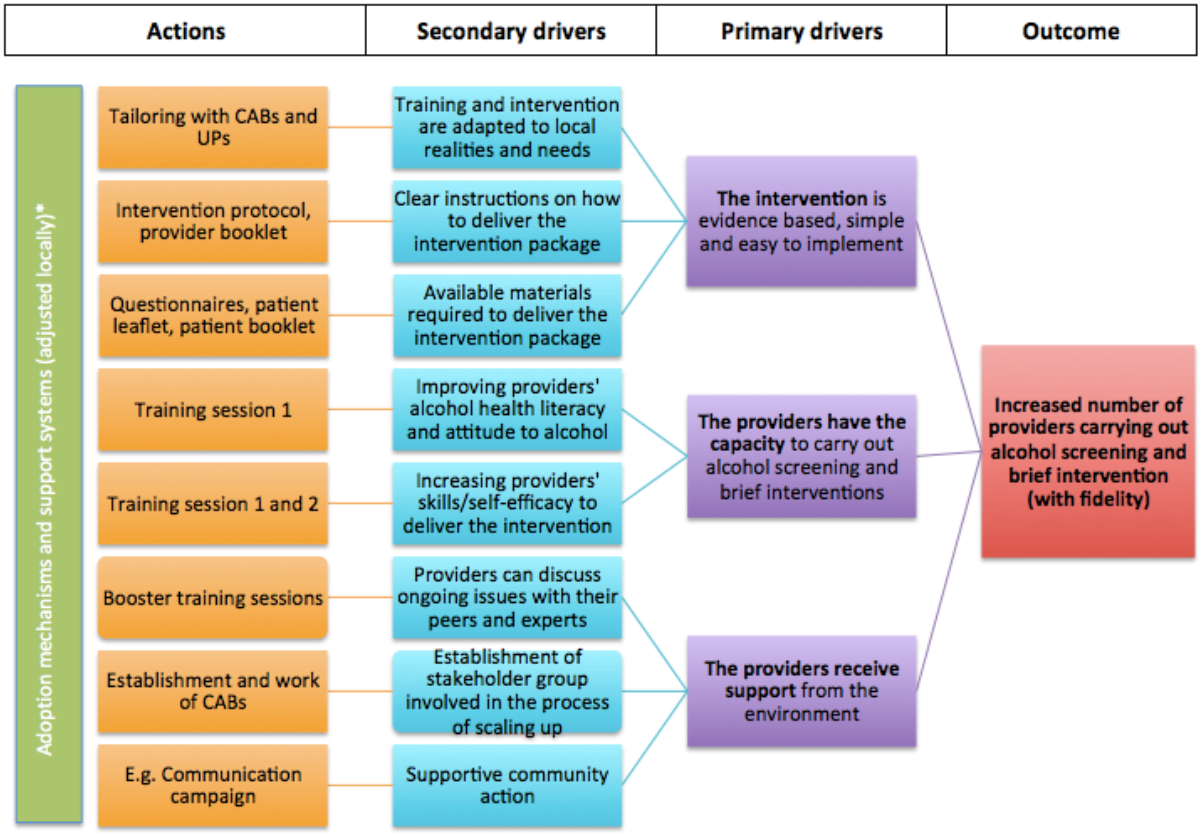

Figure 6. Driver diagram of the SCALA protocol

Barriers and facilitators assessment

Factors influencing the implementation of the SCALA protocol will be assessed before the implementation, as well as monitored throughout. The anticipated barriers and facilitators to implementation will be assessed through development of evaluation tool based on literature review[35-37] and implementation framework[10], with subsequent refinement and adaptation to the local context through focus group discussions and workshops with the CABs. The aim of the tool is to identify the barriers that would have to be addressed and monitored throughout implementation and the facilitators that would incentivize and engage providers and the PHCU unit managers in uptake and scaling up of the SCALA protocol. The experienced barriers and facilitators will be further monitored through meeting observation, provider questionnaires and interviews, as well as interviews with other involved stakeholders (e.g. CAB members, PHCU managers).

Implementation, mechanisms of impact and context

The factors influencing the progress from scale-up to outcomes will be identified and documented based on UK Medical Research Council guidance[38], analysing factors within five groups: (i) description of intervention and its causal assumptions; (ii) context; (iii) implementation; (iv) mechanisms of impact; and, (v) outcomes. All aspects of the intervention will be taken into consideration: the intervention, intervention tailoring, training, training tailoring, as well as the municipal action, consisting of the CABs and the communication campaign, combining both quantitative and qualitative methods in order to obtain a comprehensive picture of the integration and interaction of included variables. A detailed description of the topics of interest and accompanied methods is presented in Table 5.

Table 5 Process evaluation topics based on MRC guidelines

Part of process evaluation		Topic of investigation	Method
Implementation	*Adaptation*	Experience of intervention tailoring	Key informant interview
		Experience with training tailoring	Key informant interview
	Dose delivered (completeness of delivery)	Implementation of the protocol (number of screenings, brief advice given, referrals done)	Tally sheets
		Implementation of training	Observation
		Implementation of adoption mechanisms and support systems on municipal and organisational level	Key informant interview, Document analysis
		Implementation of CAB meetings	Observation, document analysis
		Implementation of communication campaign	Key informant interview, document analysis
	Fidelity (quality of implementation)	Following the care pathway as intended	Tally sheets, patient questionnaire
		Training execution	Observation
	Reach	Number of patients and providers involved	Document analysis
		Number of providers attending the training	Document analysis
Mechanisms of impact	*Participant responses*	Patients' perception of acceptability of intervention	Patient questionnaire
		Providers' satisfaction with the training	Post-training questionnaire
		Providers' perceived utility of training sessions	Post-training questionnaire
		Perception of the campaign	Provider questionnaire, patient questionnaire
		Perception of the municipal action	Key stakeholder interview
	Mediators	Influence of training on self-efficacy	Provider questionnaire
		Influence of communication campaign on beliefs and social norms	Provider questionnaire
		Perception of the attributes of the intervention	Provider questionnaire
	Unintended consequences	Possible unexpected side effects emerging	Key stakeholder interview
Context		Perceptions of organisational context	Provider questionnaire
		Individual moderating characteristics	Provider questionnaire
		Contextual factors influencing training	Observation, key informant interview
		Contextual factors influencing municipal action	Key informant interview, document analysis

The five groups will be assessed as follows:

i. *Description of the intervention.* The description of the intervention and its causal assumptions draws from the previously described driver diagram;

ii. *Implementation.* Implementation of the training delivery will be assessed though document analysis (reports from training), observation and self-reports from the trainers. Implementation of the intervention delivery will be assessed through document analysis, interviews with patients and providers. The areas of focus will be fidelity, adaptation, dose and reach. Implementation of the CAB meetings and community action will be assessed mainly through document analysis, as well as key informant interviews;

iii. *Mechanisms of impact*. The following three areas will be covered: participant responses to the

intervention, mediators and unintended consequences. Mechanisms of impact of intervention delivery will be assessed through patient and providers questionnaires. The patient interviews will focus on their responsiveness to the intervention, specifically looking at perceived acceptability. In order to evaluate participants' response to the training, post-training questionnaire examining satisfaction with the training and perceived utility of training sessions will be applied, triangulated with data from observation and trainers' self-report. Additionally, provider's self-efficacy will be tested as potential mechanism of impact that links the implementation to the outcomes. Mechanisms of impact of the CAB meetings and community action will be examined through key informant interviews and questionnaires. Specific focus will be placed on perceptions and mechanisms of actions of the communication campaign, examining its effect on attitudes and social norms of both providers and patients;

iv. *Context.* Contextual factors that should be considered in order to better understand the success of the intervention will be assessed through meeting observation, document analysis, provider questionnaires, as well as stakeholder interviews, with the main focus primarily on individual and organisational level characteristics of the context. For training evaluation, context will be assessed through observation and trainers' self-report. Context of municipal level actions will be assessed through key informant interviews; and,

v. *Outcome.* The data collected through process evaluation will be combined with the outcomes and presented within the RE-AIM[39-41] framework, evaluating SCALA's impact across the dimensions of reach, effectiveness, adoption, implementation and maintenance, Figure 7, next page.

Contextual and policy factors

Based on methodology of Ysa et al[42], contextual and policy factors on national and municipal level will be identified through document analysis and key informant interviews. The main variables considered for contextual analysis will be: (1) available data similar to that of the OECD better life initiative[18]; (2) Sustainable Governance Indicators[19]; and, (3) World Values Survey data[20]. For policy analysis, the information sought will be for a for alcohol policy-related strategies, action plans, legislation and evaluations, both on country and municipal level. The existing contextual and policy factors will be mapped onto the test of the scale-up of the SCALA package to describe and identify those factors that might influence going to full-scale beyond the tested scalable units.

Figure 7 RE-AIM dimension and SCALA aims, activities and main outcome/process measures.

Outcomes

Primary outcome:
The primary outcome will be the cumulative proportion of the number of adults (aged 18+ years) registered with the PHCU that have their alcohol consumption measured with AUDIT-C.
Secondary outcomes:

- **Proportion of consulting patients who have their alcohol consumption measured by AUDIT-C:** Calculated as the number of adults who have their alcohol consumption measured by AUDIT-C divided by the total number of number of adults who consult the PHCU during the same time period per participating provider and averaged per participating PHCU;
- **At risk population receiving advice and/or treatment for heavy drinking:** Calculated as the number of adults with an AUDIT-C score of 8+ who receive brief advice and/or referral for their heavy drinking divided by the total number of number of patients with an AUDIT-C score of 8+ per participating provider and averaged per participating PHCU. Information will also be collected on the number of patients with an AUDIT-C score of <8 who receive brief advice and/or treatment for their heavy drinking;
- **Proportion of patients with AUDIT-C score of 8+ who receive assessment for depression:** Calculated as the number of consulting adults with an AUDIT-C score of 8+ who complete PHQ-2 divided by the total number of number of patients with an AUDIT-C score of 8+ per participating provider and averaged per participating PHCU;
- **At risk population receiving advice and/or treatment for comorbid depression:** Calculated as the number of adults with a PHQ-2 score of 3+ who receive a patient leaflet and/or referral for their depression divided by the total number of number of patients with a PHQ-2 score of 3+ per participating provider and averaged per participating PHCU; and,
- **Provider attitudes:** Attitudes of the participating providers will be measured by the short version of the Alcohol and Alcohol Problems Perception questionnaire, SAAPPQ[22]. The responses will be summed within the two scales of role security and therapeutic commitment. Individual missing values for any of the items in a domain will be assigned the mean value of the remaining items of the domain before summation.

Statistical tests of key hypotheses
Primary study goal: Multilevel regression analyses will be undertaken at 12 months' time of the implementation test period, using cumulative results at months 1-12, and at 18 months (using cumulative results months 13-18, and cumulative results months 1-18), with co-variates of country and results during baseline month, using focused comparisons on the primary outcome, analysed at the levels of the PHCU and provider by study arm, taking into consideration the hierarchical nature of the data. For any PHCU or provider that drops out during the study, outcome values for subsequent measurement points will be set at the last value obtained.

Hypothesis 1: comparing results on primary outcome after 18 months with results after 12 months via regression dummies (co-variates: country; baseline month).
Hypothesis 2: For months 1-12 and months 1-18, compare cumulative coverage as per primary outcome between Arms 1 and 2, analysis of co-variance (co-variates: country; baseline month).
Hypothesis 3: In the presence of clinical equivalence of a relative difference of cumulative coverage of patients screened by less than 10% by month 6 the difference between Arm 3 and Arm 4, analysis of co-variance (co-variates: country; baseline month). If Arm 4 is not superior to Arm 3, both arms will be collapsed into Arm 3 from month 8 onwards.

Sample size calculations for main hypothesis
As the outcome of the primary study goal is predicted to be Arm3 > Arm2 > Arm1, we compared both

Arm 2 > Arm 1, and Arm 3 > Arm 2.

Our power calculations are based on the following assumptions: given the average size of a PHCU of 15,000 adults, with an average of 1500 new consultations per month, we expect a cumulative coverage after 12 months of 0.0325 of the registered adult population to have had their alcohol consumption measured in the control condition (Arm 1) (data extrapolated from month 3 and month 9 assessments of control group from ODHIN study[7, 21]; Anderson, personal communication). For the short clinical package and short training (Arm 2), we expect this to increase to 0.075 (data extrapolated from month 3 and month 9 assessments of training group from ODHIN study[7, 21]; Anderson, personal communication). Although the WHO Phase IV study predicts an additional beneficial impact of municipal support[14], precise empirical data is not available – however, we consider an estimate for Arm 3, with municipal support, to be 0.15, a proportion that would need to be achieved to consider municipal support to be worthwhile. To detect the difference between Arm 2 and Arm 1, assuming a design effect of 15 PHCUs (clusters) across the three municipal areas in Arm 2, with 15,000 patients (items), and 12 PHCUs (clusters) in Arm 1, with 15,000 patients (items), with an ICC for PHCUs of 0.03 (data from ODHIN study[7, 21]; Anderson, personal communication) we would have 82% power at a significance level of 5%[1]. For the difference between Arm 3 and Arm 2 (15 PHCUs/clusters in each arm), we would have 96.5% power.

DISCUSSION

This protocol outlines a quasi-experimental study[1] to test the extent to which embedding PHC-based screening and brief advice activity within supportive municipal action leads to improved scale-up of more patients with heavy drinking receiving appropriate advice and treatment.

For a wide range of health care issues, including communicable and non-communicable diseases, as well as reproductive and child health care, major variations continue to exist in many dimensions of quality of care, including safety, efficiency, effectiveness, timeliness, patient centeredness, and equity[13] . This can be understood as a failure to equitably scale up excellent care to ensure that what we know works is delivered to everyone who needs it.

There is a wealth of literature on implementation science and quality improvement, and a range of frameworks exist that include a sequential approach for scale-up, and that provide practical guidance for how to work with organizations, health systems, and communities to implement and scale-up best practices[43-50] .

In choosing a framework to adopt and apply, we wanted one that draws together: the main themes of sequencing activities to get a complex health system intervention, with elements of prevention and management, to full scale; the mechanisms that are required to facilitate the adoption of a complex health system intervention; and, the underlying factors and support systems required for successful scale-up. We also wanted a framework that includes a scalable unit at meso- (in our case city) level that provides the key infrastructural components and relationship architecture that are likely to be common across cities that are part of networks, (e.g., Healthy Cities Networks) enabling a more likely successful transition to full scale.

A key framework that meets all these needs is that of the Institute for Healthcare Improvement (IHI) which identifies adoption mechanisms and support systems for use across the steps, and identifies

[1] PASS[16] sample size software. https://www.ncss.com/software/pass/: Donner, A. and Klar, N. 2000. Design and Analysis of Cluster Randomization Trials in Health Research. Arnold. London.

the implementation methods that can be used at each step, that we have incorporated into our protocol[13] .

The proposed study has several features that merit attention. It:

1. Uses heavy drinking[51-52] as our operational approach rather than alcohol use disorder or harmful use of alcohol that can be defined differently by culture[53-54];
2. Sets a higher cut-off score for AUDIT-C (8+) than is commonly used to classify screened case-positives, matching definitions of heavy drinking[55-56], and similar to baseline levels of alcohol consumption in PHC-based trials to reduce heavy drinking[57] . We also set the same cut-offs for men and women, based on epidemiological evidence[58] , and minimizing unintended consequences of using different cut offs for men and women[59] ;
3. Tests for non-superiority of implementing a standard measurement and 5-minute brief advice programme with six hours of training compared with implementing a shorter 1-minute brief advice programme with three hours of training , recognizing the evidence suggests that brief advice is as effective and cost-effective as more extended advice or treatment in reducing heavy drinking[60-63], and the need for very brief clinical and training programmes for time-constrained providers;
4. Recognizes the importance of comorbid moderately severe and severe depression[64-66] , by building in identification and referral mechanisms, recognizing that moderately severe and severe depression can be well-managed with sufficient support systems in PHC[67-69] ;
5. Based on evidence[14] , adopts a novel approach by embedding and scaling-up the PHC activity within cities, supported by a series of city-based adoption mechanisms and support systems[13] , and enhanced alcohol health literacy[70] , aiming to assist in building a new knowledge base, on which better policy could be based;
6. Uses a theory-based approach to tailoring[8-10] , creating city-based Community Advisory Boards, and user-based UPs to ensure that tailoring matches user needs, municipal services[71] , and co-production of health[72] ;
7. Has a longer time frame (18 months) than is traditionally used in implementation studies[7, 21, 73-74] , to assess longer term impacts;
8. Gives considerable emphasis to process evaluation[38] , developing logic models to document the fidelity of all implementation strategies, and to identify, the drivers and barriers and facilitators to successful implementation and scale-up, and the political and economic contextual factors that might influence scale-up, based on the RE-AIM framework[39]; and,
9. Places the study design and materials in the public domain, so that others might replicate the study approach (with acknowledgment) to see if the scale-up principles can work across jurisdictions. In so doing, we would be pleased to receive comment and feedback.

We are aware of some limitations of the study design. As we are unable to randomize the involved cities, we adopt a quasi-experimental design, recognizing that it is not possible to randomly allocate the municipalities. Randomized selection of the municipalities was excluded as the hypotheses and the study approach relies on municipal-level interventions. A trial with random assignments of municipalities is not feasible due to cost (number of municipalities) and municipal-based political and technical considerations. Randomization of primary health care centres within municipalities is also impossible for the same reasons of municipal involvement in the interventions. Clean comparator conditions in this environment where the municipality supports primary health care-based does not seem to be possible. As a result, we created a quasi-experimental design[1], trying to optimize comparator for confounding, and using propensity score matching (PSM), given the above constraints. While full comparator via randomization, and thus establishment of causality is not possible, together with the qualitative evaluation component of the study, we will be able to clearly identify the

mechanisms which were crucial in leading to the outcomes. According to a recent 7-item checklist for classifying quasi-experimental studies for Cochrane reviews[75], our approach is, nevertheless, ranked as a strong design.

Although our focus on embedding PHC activity within supportive municipal actions is hypothesized to increase screening and brief activity over and above that previously demonstrated, such an approach also brings risks. Municipal governments change; and, thus health priorities may change. Although our approach minimizes the need for extra resources (and in some jurisdictions, could be resource saving[76-77]), it is not resource free. Funding constraints could limit future scale-up and sustainability.

We have adopted two approaches to promote sustainability. First, our protocol is based on transdisciplinary research, which is an approach that: identifies, structures, analyses, and deals with specific problems in such a way to grasp the complexity of problems[78]; takes into account the diversity of life-world and scientific perceptions of problems; links abstract and case-specific knowledge; and, develops knowledge and practices that promote what is perceived to be the common good[79]. As such, we involve municipalities as stakeholders to form explicitly orchestrated and managed ecosystems that cross organizational boundaries. Municipalities will create an appropriate engagement platform that provides the necessary environment, including people and resources, for sustainability. Second, we have chosen municipalities as the level of scale, making use of the existing Latin American and Caribbean (LAC) Healthy Cities Network as a natural platform for going to full-scale.

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