

Title

Co-DIRECT Nepal: a community-based diet programme for remission of type 2 diabetes and amelioration of non-communicable disease risks: study protocol for a randomized controlled trial.

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Abstract

Background:

Type 2 diabetes (T2D) prevalence is rising in low- and middle-income Asian countries, with high morbidity, mortality and healthcare costs. While medications remain central to management, recent evidence demonstrates remission of T2D through weight loss with contextual dietary interventions. The present study, in Nepal, evaluates a culturally appropriate, low-cost, dietary intervention delivered through existing community infrastructure, with minimal health-professional involvement.

Methods and analysis:

This study adopts a Type-I hybrid effectiveness-implementation design. A randomized controlled trial will assess 4-month remission outcomes, followed by 12 months of observational follow-up. Participants diagnosed at community-screening will be allocated to either immediate intervention, or a control group who will receive the intervention after a 4-month delay. The intervention comprises a dietary plan of ~850 kcal/day for weight loss induction, followed by 1200-1500 kcal/day for weight maintenance, delivered by local health workers, with counselling and home visits by female community health volunteers. The primary outcome is T2D remission at 4 months, assessed by fingerprick HbA1c. Secondary outcomes include changes in body weight, blood pressure, handgrip strength, and quality of life, for all 120 participants over 12-months follow-up after receiving the intervention. Implementation Research outcomes focus on reach, acceptability, appropriateness, feasibility, adoptability, and long-term sustainability. Findings will be disseminated through peer-reviewed journals, relevant institutional websites and scientific meetings.

Trial registration: ISRCTN14042582

Strengths and Limitations

- First community-based, culturally tailored dietary intervention trial for type 2 diabetes remission in Low- and Middle-Income Countries, delivered through existing community health structures, to support feasibility and sustainability.
- Mixed-methods design enables assessment of effectiveness alongside implementation outcomes.
- Strong governance and scientific rigour through co-design, multi-level stakeholder engagement and an established multidisciplinary national and international research collaboration.
- Convenience sampling of primary health care facilities to run T2D screening and research may limit generalisability and introduce selection or social desirability bias.
- Random allocation to treatment or control reduces risk of bias through convenience sampling of community healthcare facilities.
- Intervention contamination due to participant mobility may reduce apparent effectiveness of the intervention.
- Designating 'no-remission' to participants lost to follow-up avoids bias avoids the exaggeration of benefits inherent in a completers analysis

Introduction

Diabetes is a rapidly growing global health burden, affecting an estimated 589 million adults aged 20–79 years in 2024 and causing approximately 3.4 million deaths worldwide. The prevalence is projected to rise to 853 million by 2050, with global health expenditure exceeding USD 1 trillion, representing a 338% increase over the past 17 years.¹ Notably, 81% of individuals with diabetes reside in low- and middle-income countries (LMICs).¹ In South East Asia, 107 million adults were living with diabetes in 2024, projected to reach 185 million by 2050, with one of the highest proportions of undiagnosed cases (42.7%) and only USD 12 billion in diabetes related expenditure highlighting the urgent need for strengthened prevention and management strategies.^{2,3}

Nepal, one of South Asia's poorest countries, has undergone a marked epidemiological transition, with NCDs now the leading causes of death and a substantial rise in both

prevalence and diabetes-related mortality.⁴ National diabetes prevalence among adults aged 20–79 years is estimated at 7.7%, with 2,776 diabetes-related deaths and an average annual cost of USD 91.4 per person.⁵ Key drivers of type 2 diabetes (T2D) include rapid urbanisation, population ageing, declining physical activity, and increasing consumption of ultraprocessed foods.⁶ Progression from prediabetes to T2D is particularly frequent among Asian populations, yet well recognised as preventable through modest weight loss.⁷

Evidence from the DiRECT trial demonstrated that T2D can be reversed through dietary weight loss: remission (HbA1c <6.5% without medication) were achieved by 46% at one year, rising to 70% with loss >10kg (>10%) and over 80% with loss >15kg.^{8–10} The intervention also reduced blood pressure and medication use¹¹, improved pancreatic function, and proved cost effectiveness.¹² Five-year follow-up confirmed frequent sustained remission if weight loss was maintained, acceptable adverse event profiles, and improvements in quality of life.¹³ Similar outcomes were reported in the DIADEM-1 trial (61% remission rate),¹⁴ and the STANby trial in South Asians (40% remission, average weight loss of 8%).¹⁵ These findings, and similar results from trials in Australia and Singapore, have informed routine clinical adoption of 'DiRECT principles' for T2D remission within the National Health Services in the UK and elsewhere.^{16, 17}

Internationally, Sustainable Development Goal (SDG) target 3.4 aims to reduce premature NCD mortality by one-third by 2030.¹⁸ Nepal has incorporated NCDs into national policy through Nepal Health Sector Plan (NHSP II) and a National Multi-Sectoral Action Plan^{19–20} and the Nepal National Health Policy 2019 specifically addresses urban migration and associated T2D risk.²¹ However, the health system remains predominantly focused on infectious diseases, with limited NCD investment, inadequate routine screening, and restricted access to specialist diabetes care.^{22–25} Furthermore, reliance on indigenous practices and unproven herbal treatments for diabetes heightened during COVID-19 pandemic has contributed to delayed care, early complications, and substantial financial burden.²⁶

Given robust evidence supporting structured dietary weight-loss interventions for T2D remission, a usual-care, i.e. no-intervention, control arm was considered ethically inappropriate. This study therefore employs a delayed-intervention comparator, whereby participants receive the same intervention after a four-month delay, ensuring equitable access while enabling assessment of early versus delayed implementation. This design also reflects real-world constraints of resource-limited health systems. Building on our pilot hospital-based study, HoDIRECT-Nepal,²⁷ which demonstrated that a traditional food-based approach can improve glycaemic control and achieve T2D remission, the current study will evaluate a community-level screening and dietary intervention model, aiming to develop a scalable, culturally acceptable approach for semi-urban populations in Nepal and other LMICs.

Methods and analysis

This protocol was developed and reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 checklist (given in supplementary information).²⁸

Study design

This is a prospective, community-based, hybrid effectiveness-implementation study, guided by a novel Merged Implementation Science (MIS) framework, developed by "merging" the Consolidated Framework for Implementation Research (CFIR)²⁹ and PARiHS framework.³⁰ The study will assess both primary and secondary clinical outcomes alongside implementation outcomes, to determine whether a community-based dietary intervention can be effectively adopted, delivered, and sustained in real-world settings. A mixed-methods approach will ascertain implementation outcomes, while clinical effectiveness will be assessed through a multi-site, open-label, two-armed, individually randomized controlled trial (RCT) conducted under intention-to-treat (ITT) principles. Participants will be allocated to either an immediate intervention group or delayed intervention (control) group, with the latter receiving the same intervention after a four-month delay.

Study Objectives

This study aims to evaluate a proven dietary intervention for T2D remission and NCD risk reduction, culturally adapted for semi-urban populations in Nepal. Specifically, the study seeks to: (1) document the effectiveness and effect sizes of T2D remission outcomes; (2) record and evaluate participant and community experiences of implementation, identifying barriers, incentives, and the need for further cultural adaptations; (3) optimize program implementation with respect to cultural context, local leadership, and appropriate approaches to evaluation and audit; (4) identify opportunities to enhance implementation reach, scalability, and sustainability by considering staff roles, knowledge, attitudes, and skills; (5) prepare the ground for future program expansion through policy, practice, and public awareness of NCD risk factors; (6) determine broader sustainability considerations such as food security and urbanization; and (7) co-create, with Nepali stakeholders, a novel evaluation-oriented framework tailored to T2D remission implementation in LMIC urban community environments.

Study site

The study will be implemented across three municipalities (Dhulikhel, Banepa, and Panauti)- located in Kavrepalanchowk district of Bagmati Province, Nepal (Figure 1). Dhulikhel, situated approximately 30 km east and recognised as Nepal's first 'healthy city', has a population of 33,726 and 15 primary healthcare facilities.³¹⁻³² Banepa, approximately 26 km east of Kathmandu, is the smallest municipality in the district by area but the most populous with 67,690 residents and 14 basic health service centres.³³ Panauti, approximately 32 km southeast of Kathmandu, has a population of 51,504 and 12 health facilities.³¹

Study participants

The study population comprises adults aged 30-65 years from semi-urban communities, identified through community-based screening. Eligible participants are residents willing to provide informed consent, BMI >23 kg/m² and who meet at least one of the following criteria: (i) prediabetes (HbA1c 39–47 mmol/mol i.e., 5.7%-6.4%), (ii) previously diagnosed type 2 diabetes (HbA1c ≥48 mmol/mol i.e., >6.5%), not on glucose-lowering

medication for at least six months, (iii) a family history of T2D, and/or a history of gestational diabetes. Exclusion criteria include current use of glucose-lowering medication, planning pregnancy, pregnancy or lactation, comorbidities which limit dietary adherence, planned migration from the study area within one year.

Power and Sample size

Power calculations are based on published RCTs of T2D remission (DiRECT, DIADEM-1, and STANDby)^{8, 14, 15} and the Nepal pilot study.²⁷ Anticipating a mean weight loss of 4 kg at four and drawing on regression data¹⁵, a 4% weight loss is associated with an expected remission rate of 20% at 12 months. Given that the study targets newly diagnosed patients and that remission rates are likely higher at earlier time points, a remission rate of 25% at four months in the intervention group and 5% in the control group was assumed. To achieve 80% power to detect this difference at 4 months, a total of 120 participants with equal allocation is required. Assuming, participants lost to follow-up are not in remission, no additional sample size inflation was applied, ensuring a conservative analysis. In Nepal, prediabetes prevalence is estimated at 9.2%.²⁴ Targeted community screening is expected to identify 15–20% of individuals with prediabetes, yielding approximately 100 eligible participants from 800–1000 screened adults. Qualitative data will be generated through in-depth interviews with approximately 30 key stakeholders across government, professional bodies, community groups, and implementing staff, alongside focus group discussions (8–10 participants from each trial arm) to explore implementation processes and contextual factors.

Randomisation and Allocation Concealment

A total of 120 participants diagnosed with T2D will be individually randomised (Figure 2) using computer-generated block randomisation prepared by an independent statistician. Allocation concealment will be ensured through sequentially numbered, opaque, sealed envelopes opened only after enrolment and baseline assessments. Household members who enrol together and screen positive will be randomised to the same study arm, with clustering accounted for in the analysis if required. Participants will be allocated in the presence of a health worker, and study staff will be instructed not to disclose allocation

or provide support to delayed-intervention participants. All enrolled participants will receive a 'study passport' card containing personal demographic information, individual trial timetable and key data.

Intervention

The dietary intervention is adapted from the HoDiRECT- Nepal pilot study ²⁷ and comprises two phases: an initial Total Diet Replacement (TDR) phase (0–8 weeks) providing ~850 kcal/day to achieve ≥10 kg weight loss, followed by a weight-maintenance phase (8–52 weeks) providing ~1,235 kcal/day. Both phases are based on locally available, culturally appropriate foods.

The intervention will be delivered at participating health facilities by trained local health workers, supported for on-the-job training by a research assistant, dietitian, and medical officer, with involvement of FCHVs. At the initial face-to-face counselling session, participants attend with a family member to strengthen household support for dietary change. Clinical assessments including blood pressure, body weight, and handgrip strength are conducted, and participants will receive structured education on diabetes remission alongside detailed dietary counselling using a remission diet manual and a printed diet plan. Locally appropriate portion measurement tools and home weighing scale, marked with individual target weight, are provided. Participant understanding will be assessed using a teach-back approach and contact information for between-visit support will be shared.

Weight-loss targets are individualised to approximately 10% below baseline weight: ≥100 kg, target 15 kg loss; 90–99 kg, target 10 kg loss; 80–89 kg, target 8 kg loss; and 60–79 kg, target 7 kg loss. Participants will attend monthly follow-up visits at the health facility over 12 months, and the assessment information will be recorded on a participant-held 'study passport' card. During the first month, FCHVs will conduct two home visits (two and four weeks); thereafter, monthly home visits will continue. A structured visit form will be completed at each home visit, and the research assistant will conduct follow-up phone calls to monitor participants' condition and progress and to identify issues requiring earlier

attention. Participants will be encouraged, where feasible, to photograph meals and share them with the research team.

A predefined monitoring and escalation algorithm is in place: if blood glucose exceeds 11 mmol/L, HbA1c will be measured. If HbA1c has fallen, participants will be encouraged to continue weight-loss efforts; If HbA1c has risen without > 8 kg weight loss, barriers will be assessed and addressed; If HbA1c has risen despite > 8 kg weight loss, the participant will be referred to a tertiary hospital care. To minimise attrition, participants who miss follow-up visits will be contacted by health workers and FCHVs. All adverse events will be systematically documented, and a Trial Steering Committee (TSC) will oversee implementation and governance.

Intervention implementation plan

Implementation will follow a structured four-component plan. First, health workers and FCHVs will be trained using a manual adapted from the WHO PEN protocol and tailored to the local context, covering diabetes basics, low-calorie diet delivery, HbA1c measurement, use of dynamometer and weighing equipment, and counselling skills. Dietary training will be delivered by a dietitian using practical demonstrations with local tools, and training efficiency will be assessed through pre-and post-tests. Second, community HbA1c screening campaigns will be organised across 2–3 locations per ward, with awareness raised through FCHVs, household visits, flyers, posters, and social media.

Screening will include demographic and clinical data collection with eligible individuals receiving finger-prick HbA1c testing using the validated, portable, Afinion-2 meter (Abbott).³⁵ Quality control will be managed by the biochemistry department at Dhulikhel Hospital using Abbott methods, and by comparison with laboratory method. Screening data will be used to develop diabetes and prediabetes Risk Scores for Nepal to inform future screening programmes. Third, study medical officers will provide standardised counselling and referral for newly diagnosed individuals found to have HbA1c >9%.. Fourth, participants and family members will attend a group orientation session (40–50

minutes) delivered by doctors and dietitians using interactive discussion. Detailed standard operating procedures (SOPs) will be developed for each component to ensure consistency and fidelity across sites.

Study variables

Independent variables for the randomised trial include : personal characteristics (age, sex, rank, education, wealth, ethnicity, lifestyle); ?? literacy?? Height, weight, HbA1c, blood pressure, handgrip strength and quality of life (Nepal tool.....

Independent variables for the overall hybrid effectiveness-implementation project include community characteristics (community involvement, community's beliefs, cultural practices, and dietary habits, availability of traditional foods, promotion of traditional, indigenous, "forgotten" foods, public awareness and attitudes towards traditional foods); intervention characteristics (mode of delivery, fidelity, adaptability, acceptability, perceptions on the intervention's relative advantage, complexity, costs, barriers and incentives); and farming initiatives (niche farming opportunities, novel urban farming technologies, food security, environmental impact). Dependent variables encompass health outcomes and implementation outcomes.

Outcomes and its assessment

The primary clinical trial outcome is T2D remission at 4 months, defined by finger-prick HbA1c < 48mmol/ml without glucose-lowering medication following initiation of the weight loss induction diet. Secondary clinical outcomes include changes in body weight, handgrip strength (both hands, best of 3 attempts), and blood pressure at four months, changes in HbA1c, remission rates, body weight, handgrip strength, blood pressure and quality of life during 12-month observational follow-up across all 120 participants (see table 1).

Implementation outcomes include reach, acceptability, appropriateness, feasibility, adoptability, implementation fidelity and long- term sustainability. Process evaluation will assess reach, dose and fidelity of the intervention and explore how contextual variations

and stakeholder perceptions influence outcomes. Impact metrics include number of community health supporters and volunteers trained, and numbers of individuals self-presenting for screening after formal recruitment ceases. The inclusivity and equitability of community screening including effectiveness of awareness raising activities to attract volunteers 3000-4000 for HbA1c screening and equitability of programme adherence and health benefit will be evaluated. Continuous improvement methods will be used throughout to optimise reach, engagement, programme adherence and participant retention. Cost effectiveness at four and 12 months will be evaluated from a societal perspective using a cost utility analysis.

Data collection plan

Quantitative data will be collected using a structured questionnaire alongside the EuroQol-5D-5L (EQ-5D-5L) instrument to assess health-related quality of life, using the validated Nepali version.³⁴ Anthropometric measurements will include height (portable standard stature tape), weight (Camry digital weighing scale, ISO 9001 certified), and blood pressure (Medtech, Novacheck BP-18 automated device). Handgrip strength will be measured seated, three times in both hands using ???equipment. Glycaemic control will be assessed using point-of-care HbA1c testing with a regularly calibrated validated Afinion-2 meter (Abbott).³⁵ Quantitative data will be collected through paper-based, face-to-face interviews at baseline, four months, and twelve months by trained research assistants

Qualitative data will be collected through face-to-face in-depth interviews and focus group discussions (FGDs) using study-specific, semi-structured guides to explore participant and stakeholder perceptions of acceptability and feasibility. Where face-to-face interviews are not feasible, reasons will be recorded and telephone interviews will be conducted with participant consent. Interviews and FGDs will be audio-recorded with permission, supplemented by detailed field notes,

All data collection tools will be pretested prior to study implementation. Questionnaires not previously validated in Nepal will be pretested in a comparable peri-urban setting

outside the study sites. Qualitative tools will be translated into Nepali, back translated into English to ensure equivalence, and pretested to refine wording and cultural relevance. Participant retention will be supported through close coordination with health workers and FCHVs and regular follow-up phone calls.

Analysis Plan

Analyses will primarily focus on participants with baseline HbA1c levels of 48–75 mmol/mol (6.5–9.0%), the primary study population. Participants with baseline HbA1c >75 mmol/mol (9%) will be analysed separately, while secondary analyses will include all participants with HbA1c $\geq$ 48 mmol/mol (6.5%). Baseline characteristics will be summarised using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. The primary outcome of T2D remission will be analysed using an ITT approach, with comparisons between groups using chi-square tests and, where appropriate, logistic regression. Missing remission data will be assumed conservatively as not in remission, with sensitivity analyses performed using multiple imputation. For 12-month follow-up, changes in HbA1c and remission status will be analysed using repeated measures analysis of variance (ANOVA). Associations between weight change and diabetes remission will be explored using Pearson correlation coefficients and multivariable regression models. Cost-utility analysis will be conducted by converting EQ-5D-5L responses into utility scores to estimate quality-adjusted life years (QALYs) and calculate incremental cost-effectiveness ratios. Statistical significance will be set at $p < 0.05$, with results presented alongside 95% confidence intervals. All analyses will be performed using Stata version 14 (StataCorp, USA).

Plan for trial supervision and monitoring

Given the low-risk nature of the dietary intervention, no formal data safety monitoring board (DSMB) is planned. The study will be implemented under direct supervision of the principal and co-investigators and a project coordinator, supported by trained research assistants. Weekly meetings will address operational challenges, and a Study Management Group (SMG) of academic and clinical collaborators will meet monthly.

A Steering Committee including principal investigators under an external chair and members including , statisticians, municipal and government stakeholders, and community representatives will review six-monthly progress reports and any serious adverse events.

Patient and public involvement

Patients and the public were involved at the early conceptualisation stage of the research through insights generated from the HoDiRECT-Nepal ²⁷ pilot study.

Ethics and Dissemination

Ethical approval was obtained from the Nepal Health Research Council (Reg. no. 440/2024) and the University of Glasgow (Reg. no. 200240032). Written and verbal informed consent will be obtained from all participants prior to data collection. Add methods used for consenting here (as in the ethics submission). Confidentiality will be strictly maintained, with participant identifiers stored separately from study data in a password-protected system, linked only through alphanumeric codes. The study was prospectively registered in the UK's clinical study registry ISRCTN (<https://www.isrctn.com/ISRCTN14042582>) on 14 May 2025. Any protocol modifications will be approved by the relevant ethics review boards. Findings will be disseminated through publications and presentations at academic meetings and conferences. To enhance public engagement, and policy uptake, a short documentary film in Nepali and English will be produced to communicate the Co-DIRECT Nepal approach.

Discussion

CoDirect was designed for funding from the UK Medical Research Council (MRC) as part of the Global Action for Chronic Disease (GACD) Healthy Cities Programme, whose major focus is on Implementation Research in Low- and Middle-Income Countries. This study protocol demonstrates how a community-based dietary programme, culturally adapted from consistent trial evidence in High Income Countries, can operationalize T2D remission strategies in semi-urban Nepal. Building on evidence from the DiRECT trial,⁸⁻¹³ DIADEM-1 ¹⁴, and STANDBy,¹⁵ the intervention translates weight-loss-induced

remission into a locally relevant model using traditional foods and existing community health structures. By embedding the programme within these systems and leveraging FCHVs, it addresses critical gaps in routine NCD care and offers a scalable approach for LMICs.

The study novelty lies in adapting remission-focused dietary interventions to the Nepalese LMIC context. While global frameworks emphasise urgent NCD action¹⁸, and Nepal has adopted relevant national policies¹⁹⁻²¹, implementation remains limited. Health systems continue to prioritise infectious diseases, with insufficient staff or resource investment for effective or comprehensive NCD prevention and care.^{22-25,32} Routine screening is largely absent, and specialist diabetes care remains inaccessible to most of the population. In this context, reliance on indigenous practices and ineffective herbal treatments has re-emerged.³⁶⁻³⁷ This study offers an evidence-based, culturally acceptable, low-cost, and potentially sustainable alternative.

Even modest weight loss improves glycaemic control and reduces NCD risks.⁷ Our pilot HoDiRECT-Nepal study demonstrated that traditional food-based weight management can achieve T2D remission for about one third of people with relatively long-standing and poorly controlled.²⁷ The current study extends this to the community level, aiming to reduce complications, improve quality of life, and lower long-term healthcare costs, but with minimal health-professional involvement. Avoiding manufactured and imported foods, and incorporating and celebrating traditional diets and “forgotten” crops, further aligns the program with sustainability and food security principles.

Beyond clinical outcomes, the study provides a replicable model for integrating remission-focused interventions into primary care, supported by local leadership and community health workers. Such integration can strengthen NCD programmes and contribute to achieving the UN SDG target of reducing premature NCD mortality by one-third by 2030.¹⁸ By co-creating an evaluation-oriented framework with Nepalese stakeholders, the study will generate transferable insights into barriers, incentives, and adaptations necessary for successful implementation across similar low-resource settings.

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Authors' contributions

ML, BMK, AS, SS, CN, NS, and JB contributed to the conceptualization and design of the study. ML was responsible for trial registration, while BMK, AS, and PR were responsible for obtaining ethics approval. The intervention was developed by CN and SK. SS, CN, LPP, and AzS contributed to the design and analysis of the implementation research. RAS contributed to the design and analysis of the cost-utility evaluation. AT, JS, SL, and SSp will be responsible for data collection. BMK, AS, RS, PR, and AT will be responsible for monitoring the implementation of the trial. AMcC, and AMcI will be responsible for the statistical analysis. The primary manuscript was drafted by PR and RAS. All authors contributed to the review and editing of the manuscript. All authors had full access to the study data and approved the manuscript for submission for publication.

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Competing interests: None declared

Tables and Figures

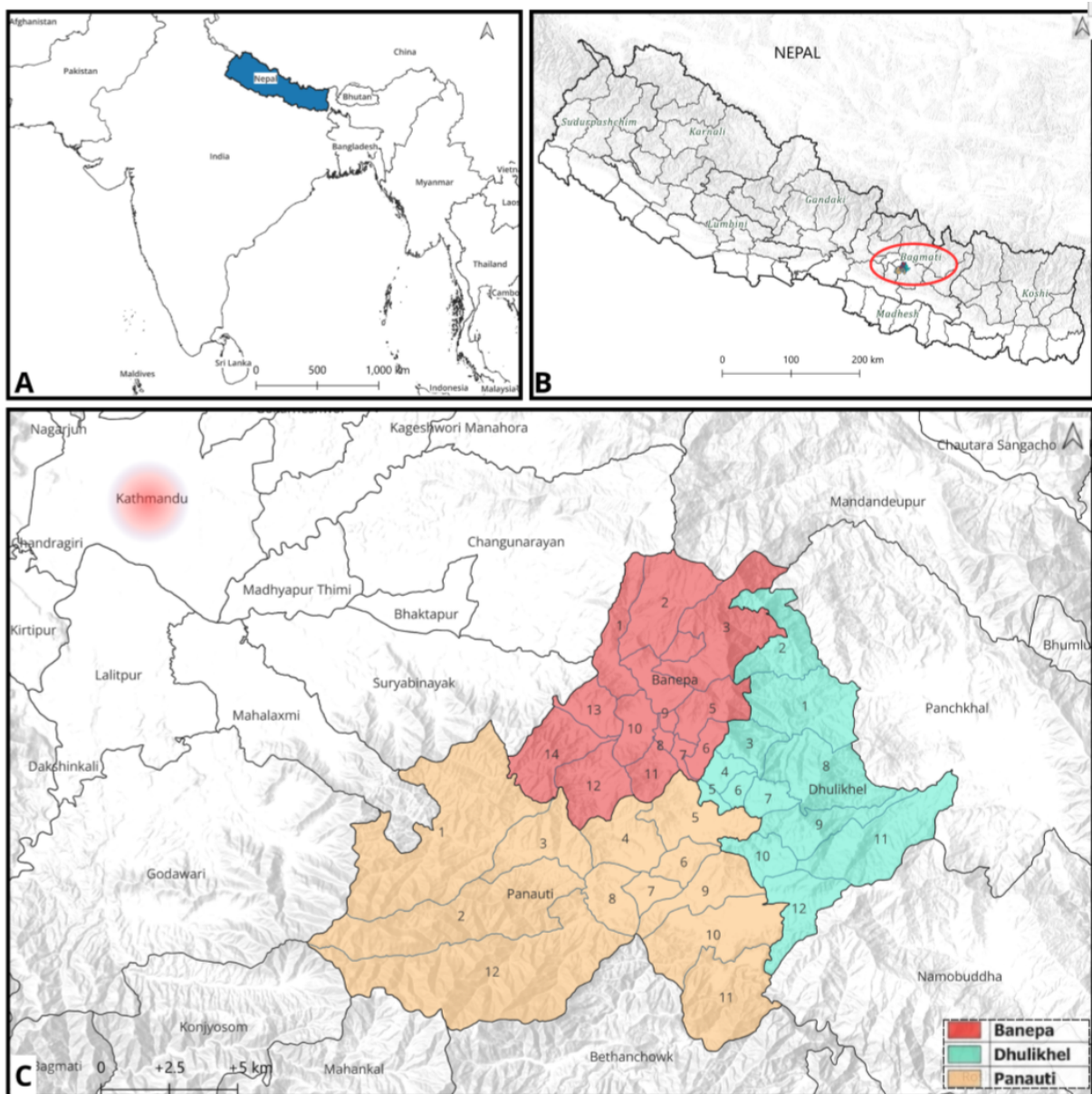


Figure 1. Location of the study area: (A) Regional context of Nepal in South Asia; (B) Map of Nepal highlighting the Bagmati Province; (C) Detailed administrative map of Banepa, Dhulikhel, and Panauti municipalities with ward-level divisions and local topography

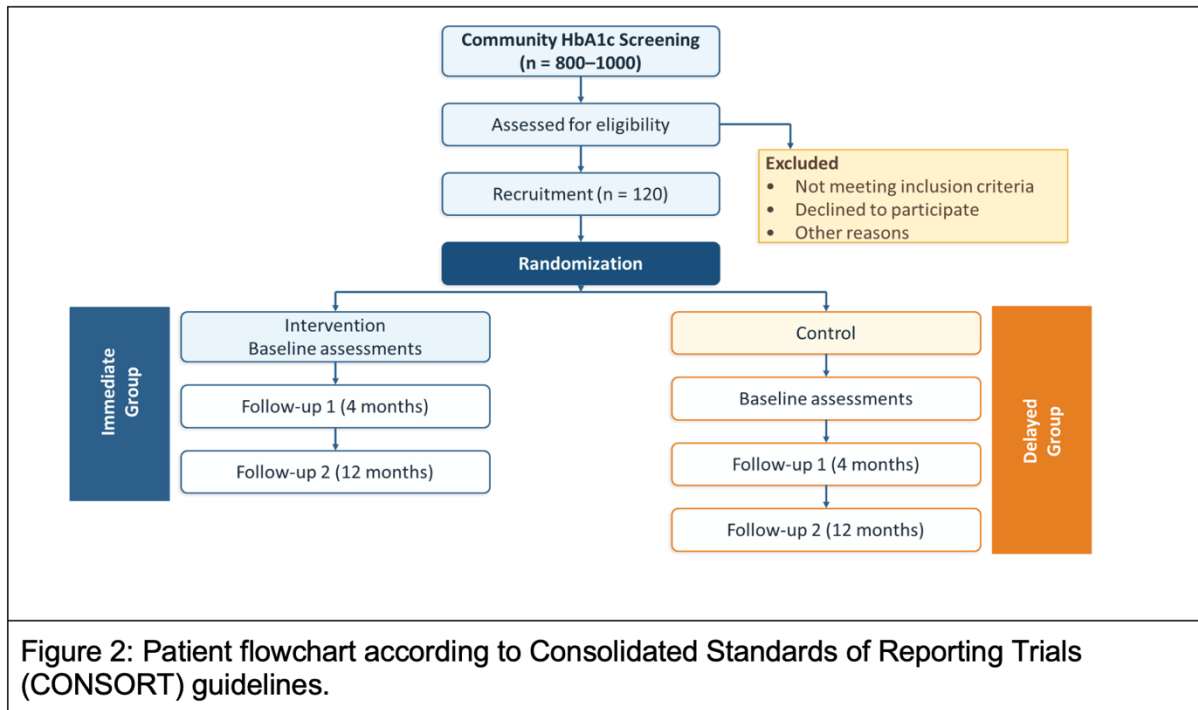


Figure 2: Patient flowchart according to Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Table 1. SPIRIT schedule of enrolment, interventions, and assessments for the Co-DIRECT, Nepal trial.

Study Period	Enrolment	Allocation	Post-allocation	Post-allocation	Post-allocation	Post-allocation
Time point (months)	-t1	0	4 (t1)	8 (t2)	12 (t3)	16 (t4)
ENROLMENT						
Eligibility screening	X					
Informed consent	X					
Randomisation	X					
INTERVENTIONS						
Immediate intervention arm		X				
Delayed intervention arm			X			
ASSESSMENTS						
Baseline socio demographic and clinical measures	X					
First outcome(s) immediate arm			X			
First outcomes (s) delayed arm				X		
Second outcome(s) assessment and close-out of immediate arm					X	
Second outcome (s) assessment and close out of delayed intervention arm						X
Qualitative assessments of immediate arm			X		X	
Qualitative assessments of delayed arm				X		X

Supplementary information

Table 1: Compliance of CO-DiRECT trial protocol with the Standard Protocol Items for Randomized Trials (SPIRIT) checklist

Section / Topic	No	SPIRIT 2025 checklist item description	Reported on page no.
Administrative information			
Title and structured summary	1a	Title stating the trial design, population, and interventions, with identification as a protocol	1
	1b	Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set	1-2
Protocol version	2	Version date and identifier	2
Roles and responsibilities	3a	Names, affiliations, and roles of protocol contributors	13
	3b	Name and contact information for the trial sponsor	13
	3c	Role of trial sponsor and funders in design, conduct, analysis, and reporting of trial; including any authority over these activities	13
	3d	Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable	NA
Open science			
Trial registration	4	Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry	11

Protocol and statistical analysis plan	5	Where the trial protocol and statistical analysis plan can be accessed	10-11
Data sharing	6	Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible	11
Funding and conflicts of interest	7a	Sources of funding and other support (e.g., supply of drugs)	13
	7b	Financial and other conflicts of interest for principal investigators and steering committee members	13
Dissemination policy	8	Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., reporting in trial registry, plain language summary, publication)	11-12
Introduction			
Background and rationale	9a	Scientific background and rationale, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	9b	Explanation for choice of comparator	7
Objectives	10	Specific objectives related to benefits and harms	5
Methods: Patient and public involvement, trial design			
Patient and public involvement	11	Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial	11
Trial design	12	Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)	4

Methods: Participants, interventions, and outcomes				
Trial setting	13	Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial will be conducted		5
Eligibility criteria	14 a	Eligibility criteria for participants		6
	14 b	If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (e.g., surgeons, physiotherapists)		NA
Intervention and comparator	15 a	Intervention and comparator with sufficient details to allow replication including how, when, and by whom they will be administered. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed		7-9
	15 b	Criteria for discontinuing or modifying allocated intervention/comparator for a trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)		NA
	15 c	Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (e.g., drug tablet return, sessions attended)		8
	15 d	Concomitant care that is permitted or prohibited during the trial		NA
Outcomes	16	Primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final		9

		value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome	
Harms	17	How harms are defined and will be assessed (e.g., systematically, non-systematically)	11
Participant timeline	18	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	20
Sample size	19	How sample size was determined, including all assumptions supporting the sample size calculation	6
Recruitment	20	Strategies for achieving adequate participant enrolment to reach target sample size	7-8
Methods: Assignment of interventions			
Randomization:			
Sequence generation	21 a	Who will generate the random allocation sequence and the method used	6-7
	21 b	Type of randomization (simple or restricted) and details of any factors for stratification. To reduce predictability of a random sequence, other details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	6-7
Allocation concealment mechanism	22	Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned	6-7

Implementation	23	Whether the personnel who will enrol and those who will assign participants to the interventions will have access to the random allocation sequence	6-7
Blinding	24 a	Who will be blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)	NA
	24 b	If blinded, how blinding will be achieved and description of the similarity of interventions	NA
	24 c	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	25 a	Plans for assessment and collection of trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of trial instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be accessed, if not in the protocol	9-11
	25 b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-11
Data management	26	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be accessed, if not in the protocol	10-11

Statistical methods	27 a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	10-11
	27 b	Definition of who will be included in each analysis (e.g., all randomized participants), and in which group	10-11
	27 c	How missing data will be handled in the analysis	10-11
	27 d	Methods for any additional analyses (e.g., subgroup and sensitivity analyses)	10-11
Methods: Monitoring			
Data monitoring committee	28 a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and funder; conflicts of interest and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	28 b	Explanation of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Trial monitoring	29	Frequency and procedures for monitoring trial conduct. If there is no monitoring, give explanation	11
Ethics			
Research ethics approval	30	Plans for seeking research ethics committee/institutional review board approval	11

Protocol amendments	31	Plans for communicating important protocol modifications to relevant parties	11
Consent or assent	32 a	Who will obtain informed consent or assent from potential trial participants or authorized proxies, and how	11
	32 b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
Confidentiality	33	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Ancillary and post-trial care	34	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA