

STATISTICAL ANALYSIS PLAN (SAP)

Co-DIRECT Nepal: A Community-Based Diet Programme for Remission of Type 2 Diabetes and Amelioration of Non-Communicable Disease Risks

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Statistical Overview

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ABBREVIATIONS

Abbreviation	Definition
ADA	American Diabetes Association
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
HbA1c	Glycated Haemoglobin
ITT	Intention-to-Treat
LMIC	Low- and Middle-Income Country
MI	Multiple Imputation
NCD	Non-Communicable Disease
OR	Odds Ratio
PP	Per-Protocol
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation	Definition
T2D	Type 2 Diabetes
UHC	Urban Health Centre

1. INTRODUCTION

1.1 Purpose of the Statistical Analysis Plan

This Statistical Analysis Plan (SAP) prespecifies the statistical methods that will be used for the quantitative analysis of the Co-DiRECT Nepal randomised controlled trial.

The SAP specifies:

- the analysis populations;
- definitions of primary and secondary outcomes;
- statistical methods for the primary and secondary analyses;
- methods for handling missing data;
- approaches to protocol deviations;
- sensitivity and subgroup analyses;
- longitudinal analyses; and
- presentation and reporting of results.

The SAP is intended to be finalised before the primary outcome analysis.

Any changes to the methods specified in this SAP after knowledge of treatment-group outcome data will be documented, justified and identified as amendments or post hoc analyses.

2. STUDY DESIGN

Co-DiRECT Nepal is a single-centre, open-label, two-arm, individually randomised controlled trial.

Participants will be randomised in a planned 1:1 allocation to one of two groups:

1. **Immediate intervention group:** participants receive the dietary intervention immediately following baseline assessment and randomisation.
2. **Delayed intervention group:** participants serve as the control group during the initial four-month randomised comparison and subsequently receive the same dietary intervention after the initial four-month period.

The study is implemented in three municipalities:

- Dhulikhel Municipality;
- Banepa Municipality; and
- Panauti Municipality,

in Kavrepalanchowk District, Bagmati Province, Nepal.

Participants are assessed at:

- baseline;
- 4 months; and
- 12 months.

The primary treatment comparison will be conducted at **4 months**, before the delayed group receives the intervention.

The 12-month assessment will provide longer-term follow-up of the study cohort. Because participants in the Delayed group will subsequently receive the intervention, the 12-month analysis will not be interpreted as a simple comparison of continued intervention versus control.

3. STUDY POPULATION

3.1 Eligibility criteria

The study population comprises adults identified through community-based HbA1c screening in the study municipalities.

3.1.1 Inclusion criteria

Participants must:

- be aged 30–65 years;
- have a BMI >23 kg/m²;
- be residents of the study area;
- be willing and able to provide informed consent; and
- meet one of the following glycaemic criteria:
 - o newly diagnosed T2D, defined as HbA1c ≥ 48 mmol/mol ($\geq 6.5\%$) and not currently receiving glucose-lowering medication; or
 - o prediabetes, defined as HbA1c 42–47 mmol/mol, and considered at increased risk of progression to T2D.

3.1.2 Exclusion criteria

Participants will be excluded if they:

- have known T2D and are receiving regular glucose-lowering medication;
- are pregnant or lactating, or plan to become pregnant during the study period;
- have severe comorbidities or other conditions that prevent participation in or adherence to the dietary intervention;
- are planning to migrate from the study area within the following year; or
- meet any other exclusion criteria specified in the approved study protocol.

4. STUDY OBJECTIVES

4.1 Primary objective

To evaluate the effectiveness of a culturally adapted community-based dietary intervention in achieving remission of T2D at 4 months compared with a delayed intervention.

4.2 Secondary objectives

To assess the effect of the intervention on:

- body weight;
- HbA1c;
- systolic and diastolic blood pressure; and
- handgrip strength

at 4 months.

4.3 Longer-term objectives

To describe changes in:

- HbA1c;
- T2D remission;
- body weight;
- blood pressure; and
- handgrip strength

during the 12-month follow-up period.

4.4 Safety objective

To describe adverse events and other safety outcomes occurring during the intervention and follow-up periods.

5. SAMPLE SIZE

The planned sample size for the T2D randomised comparison is 120 participants, with equal allocation between the Immediate and Delayed groups.

The sample size calculation was based on previous randomised trials of T2D remission, including DiRECT, DIADEM-I and STANDby, together with pilot data from Nepal.

A remission rate of 25% at four months in the Immediate intervention group and 5% in the Delayed group was assumed. Under these assumptions, a total sample size of 120 participants provides approximately 80% power to detect the anticipated difference using a two-sided significance level of 5%.

The sample size calculation assumed that participants lost to follow-up would not be considered to have achieved remission. No additional inflation for loss to follow-up was applied.

The planned allocation ratio is 1:1.

6. RANDOMISATION AND TREATMENT ALLOCATION

Participants will be individually randomised to the Immediate or Delayed intervention group according to the prespecified randomisation procedure.

The planned allocation ratio is 1:1.

Participants will be analysed according to their randomised allocation in the primary Intention To Treat (ITT) analysis.

Any deviations from the intended allocation procedure, including errors in treatment allocation, will be documented as protocol deviations and reviewed before the Per protocol (PP) analysis.

7. OUTCOMES

7.1 Primary outcome

The primary outcome is:

T2D remission at 4 months.

T2D remission will be defined as: HbA1c <48 mmol/mol (<6.5%) at the four-month assessment without the use of glucose-lowering medication.

The outcome will be coded as:

- **Remission = Yes:** HbA1c <48 mmol/mol (<6.5%) and not receiving glucose-lowering medication.
- **Remission = No:** HbA1c ≥48 mmol/mol (≥6.5%) or receiving glucose-lowering medication.

Participants without a valid four-month HbA1c measurement will be considered not to have achieved remission in the primary analysis, as specified in the missing-data section.

8. SECONDARY OUTCOMES

Secondary outcomes at four months will include:

8.1 Body weight

- body weight at 4 months;
- change in body weight from baseline to 4 months.

8.2 HbA1c

- HbA1c at 4 months;
- change in HbA1c from baseline to 4 months.

8.3 Blood pressure

- systolic blood pressure at 4 months;
- diastolic blood pressure at 4 months;

- change in systolic blood pressure from baseline to 4 months; and
- change in diastolic blood pressure from baseline to 4 months.

8.4 Handgrip strength

- handgrip strength at 4 months;
- change in handgrip strength from baseline to 4 months.

9. 12-MONTH OUTCOMES

The following outcomes will be assessed at 12 months:

- HbA1c;
- T2D remission;
- body weight;
- systolic blood pressure;
- diastolic blood pressure; and
- handgrip strength.

Changes from baseline to 12 months will be calculated for continuous outcomes.

Changes between four and 12 months may also be described to characterise the trajectory following the initial randomised intervention period.

Because participants in the Delayed group subsequently receive the intervention, 12-month treatment-group comparisons will be interpreted in the context of this treatment crossover.

10. SAFETY OUTCOMES

All adverse events identified or reported during the study will be documented.

Adverse events will be monitored throughout the study according to the trial safety and governance procedures.

11. ANALYSIS POPULATIONS

11.1 Intention-to-Treat Population

The primary analysis will use the Intention-to-Treat (ITT) population.

The ITT population will include all participants who are randomised.

Participants will be analysed according to the treatment group to which they were randomised, irrespective of:

- adherence to the intervention;
- subsequent treatment received;
- withdrawal from the intervention;
- withdrawal from the study; or

- protocol deviations,

subject to the prespecified handling of missing outcomes.

The ITT principle will be applied to preserve the benefits of randomisation and provide an estimate of the effect of assignment to the intervention.

11.2 Per-Protocol Population

A PP analysis will be conducted as a sensitivity analysis.

The PP population will include participants who:

- were randomised;
- received the intervention according to their allocated treatment, where applicable;
- did not have a major protocol deviation considered likely to affect the primary outcome; and
- have the outcome required for the relevant analysis.

12. GENERAL STATISTICAL PRINCIPLES

All statistical analyses will be conducted using Stata version 14.

Unless otherwise specified:

- statistical tests will be two-sided;
- the significance level will be 0.05;
- 95% confidence intervals will be reported;
- continuous variables will be summarised using mean and SD when approximately normally distributed;
- skewed continuous variables will be summarised using median and IQR;
- categorical variables will be summarised using frequencies and percentages; and
- no adjustments will be made for multiple comparisons.

13. BASELINE CHARACTERISTICS

Baseline characteristics will be summarised separately by randomised treatment group.

Variables will include, where available:

- age;
- sex;
- baseline HbA1c;
- body weight;
- BMI;
- systolic blood pressure;
- diastolic blood pressure;

- handgrip strength; and
- other clinically relevant baseline characteristics specified in the study protocol.

Continuous variables will be summarised using mean (SD) or median (IQR), as appropriate.

Categorical variables will be summarised using number and percentage.

Baseline characteristics will be presented descriptively.

14. PRIMARY OUTCOME ANALYSIS

14.1 Primary analysis

The primary analysis will compare the proportion of participants achieving T2D remission at four months between the Immediate and Delayed groups in the ITT population.

The number and percentage of participants achieving remission will be presented for each treatment group.

A Pearson chi-square test will be used for the unadjusted comparison when assumptions are satisfied. Fisher's exact test will be used where expected cell counts are too small for the chi-square approximation to be appropriate.

14.2 Logistic regression

Logistic regression will be used to estimate the association between treatment allocation and T2D remission at four months.

The treatment effect will be presented as an odds ratio (OR) with a 95% Confidence Interval (CI) and p-value.

The Immediate intervention group will be compared with the Delayed intervention group.

The primary adjusted logistic regression model will include treatment group as the main explanatory variable and will adjust for pre-specified baseline covariates: baseline HbA1c, age, sex and BMI.

15. SECONDARY OUTCOME ANALYSIS

15.1 Continuous outcomes

The following continuous outcomes will be analysed:

- body weight;
- HbA1c;
- systolic blood pressure;
- diastolic blood pressure; and
- handgrip strength.

For each outcome, the change from baseline to four months will be calculated:

Change = four-month measurement – baseline measurement.

Mean change and SD will be reported for each treatment group.

An unadjusted between-group comparison of mean change will be performed using an independent-samples t-test when appropriate.

If assumptions for the t-test are substantially violated, an appropriate alternative method will be considered.

16. ANCOVA ANALYSIS

For each continuous secondary outcome, an ANCOVA model will be used to estimate the adjusted between-group treatment effect.

The model will include:

- treatment group; and
- baseline value of the corresponding outcome.

The primary adjusted estimate will be the adjusted mean difference between treatment groups at four months, with 95% CI and p-value.

17. ANALYSIS OF HbA1c

HbA1c will be analysed as a continuous outcome.

The following will be reported:

- baseline HbA1c;
- four-month HbA1c;
- mean change from baseline;
- between-group difference in change; and
- adjusted between-group difference using ANCOVA.

18. ANALYSIS OF BODY WEIGHT

Body weight will be analysed as a continuous outcome.

The following will be reported:

- baseline weight;
- four-month weight;
- mean change from baseline;
- between-group difference in mean change; and

- adjusted between-group difference using ANCOVA.

19. ANALYSIS OF BLOOD PRESSURE

Systolic and diastolic blood pressure will be analysed separately.

For each outcome, the analysis will include:

- baseline measurement;
- four-month measurement;
- change from baseline;
- unadjusted between-group comparison; and
- adjusted ANCOVA analysis controlling for baseline blood pressure.

20. ANALYSIS OF HANDGRIP STRENGTH

Handgrip strength will be analysed as a continuous outcome.

The analysis will include:

- baseline measurement;
- four-month measurement;
- change from baseline;
- unadjusted between-group comparison; and
- adjusted ANCOVA analysis controlling for baseline handgrip strength.

21. 12-MONTH LONGITUDINAL ANALYSIS

The 12-month analysis will describe changes in outcomes over time.

For continuous outcomes, including:

- HbA1c;
- body weight;
- systolic blood pressure;
- diastolic blood pressure; and
- handgrip strength,

linear mixed-effects models will be considered the preferred approach when repeated measurements are available.

The models may include:

- time;
- original randomised treatment group;
- time-by-treatment interaction; and

- baseline value of the relevant outcome.

A participant-level random intercept will be included to account for correlation between repeated measurements within participants.

The time-by-treatment interaction will be examined where appropriate.

Because the Delayed group receives the intervention after the initial four-month period, treatment-group differences at 12 months will not be interpreted as evidence of a sustained untreated control group.

22. ASSOCIATION BETWEEN WEIGHT CHANGE AND REMISSION

The relationship between weight change and T2D remission will be explored.

Correlation analyses will be conducted using:

- Pearson correlation for approximately normally distributed continuous variables; or
- Spearman rank correlation where appropriate.

Logistic regression will be used to assess the association between weight change and remission status.

Weight change will primarily be analysed as a continuous variable.

23. ANALYSIS BY BASELINE HbA1c

The principal T2D analysis population will comprise participants with baseline HbA1c between 48 and 75 mmol/mol (6.5–9.0%).

Participants with baseline HbA1c >75 mmol/mol (>9.0%) will be described separately and, where numbers permit, analysed separately.

A secondary analysis will include all eligible participants with baseline HbA1c $\geq$ 48 mmol/mol ($\geq$ 6.5%) to provide an overall assessment of the intervention among participants with T2D.

24. ANALYSIS OF PREDIABETES

Participants with prediabetes will be analysed separately.

Analyses will describe:

- change in HbA1c;
- changes in body weight;
- changes in blood pressure;
- progression to T2D; and
- maintenance of prediabetes;

25. MISSING DATA

25.1 General approach

The extent and pattern of missing data will be summarised by treatment group and assessment time.

The reasons for missing data will be documented where available.

Missing data will be assessed separately for:

- primary outcome;
- secondary outcomes; and
- 12-month outcomes.

The number and percentage of participants with missing outcome measurements will be reported.

26. MISSING PRIMARY OUTCOME

For the primary ITT analysis, participants without a valid four-month HbA1c measurement will be classified as not achieving remission.

This represents a conservative assumption and is consistent with the sample-size calculation, which assumed that participants lost to follow-up would not be in remission.

27. SENSITIVITY ANALYSIS FOR MISSING PRIMARY OUTCOME

The robustness of the primary analysis to missing-data assumptions will be examined.

Multiple imputation will be considered under a Missing At Random (MAR) assumption.

The imputation model will include variables associated with the outcome and/or missingness, as appropriate. These may include:

- treatment group;
- baseline HbA1c;
- baseline body weight;
- age;
- sex; and
- other relevant baseline measurements.

The imputation model will be assessed using appropriate diagnostic procedures, including examination of the distributions of imputed values and convergence diagnostics where applicable.

Results from the multiple-imputation analysis will be compared with the primary analysis.

28. PROTOCOL DEVIATIONS

All protocol deviations identified during the study will be documented.

Protocol deviations will be reviewed and classified before the final PP analysis.

Where appropriate, deviations will be categorised as:

- minor deviations unlikely to affect the validity of the analysis;
- major deviations potentially affecting treatment exposure or outcome assessment; and
- treatment-allocation/randomisation deviations.

Protocol deviations will not automatically result in exclusion from the ITT analysis.

29. SENSITIVITY ANALYSES

The following sensitivity analyses will be undertaken where appropriate:

29.1 Per-protocol analysis

The primary outcome will be analysed in the prespecified PP population.

29.2 Missing-data analysis

The primary outcome will be analysed using multiple imputation under the MAR assumption.

30. SUBGROUP ANALYSES

Subgroup analyses will be exploratory and will be conducted only where sample sizes permit meaningful interpretation.

Potential prespecified subgroups include:

- sex;
- age category;
- baseline HbA1c category;
- baseline BMI category;
- other clinically relevant baseline characteristics specified before analysis.

31. MODEL ASSUMPTIONS

For linear regression and ANCOVA models, assumptions will be assessed using graphical and statistical methods as appropriate.

These will include assessment of:

- linearity;
- distribution of residuals;
- homoscedasticity; and

- influential observations.

Where assumptions are substantially violated, appropriate alternative approaches may be considered.

For logistic regression, model fit and influential observations will be assessed where appropriate.

32. OUTLIERS

Extreme observations will not be removed solely because they are statistically unusual.

Potential data-entry or measurement errors will be investigated.

Valid observations will generally be retained.

Any such analysis will be reported as a sensitivity analysis.

33. REPORTING OF EFFECT ESTIMATES

For the primary binary outcome, the following will be reported:

- number achieving remission;
- percentage achieving remission;
- odds ratio;
- 95% CI; and
- p-value.

For continuous outcomes, the following will be reported:

- baseline mean (SD);
- follow-up mean (SD);
- mean change from baseline;
- between-group mean difference;
- adjusted mean difference where applicable;
- 95% CI; and
- p-value.

Effect estimates and confidence intervals will be presented alongside p-values to facilitate assessment of the magnitude and precision of treatment effects.

34. EXPLORATORY, POST-HOC AND UNPLANNED ANALYSES

Additional exploratory, post-hoc or unplanned analyses may be undertaken where appropriate. These may include analyses conducted to explore unexpected observed results, investigate

interrelationships between outcomes, generate hypotheses for future research, or respond to reviewer or editorial comments.

The rationale for any such analyses and any relevant changes to the analytical approach will be documented.

Any analyses that were not pre-specified in this SAP before knowledge of the relevant outcome data will be explicitly identified as exploratory, post-hoc or unplanned in study reports, abstracts and manuscripts.

35. STATISTICAL SOFTWARE

All analyses will be conducted using Stata version 14 (StataCorp, College Station, TX, USA).

36. CHANGES TO THE SAP

This SAP will be finalised before the primary outcome analysis.

Any substantive changes made after SAP finalisation will be documented, including:

- the date of the change;
- the section affected;
- the reason for the change.