Statistical Analysis Plan (SAP)

Phase I: Preconception

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1 List of abbreviations

ACE	Adverse childhood event
BP	Blood Pressure
BMI	Body Mass Index
CI	Confidence interval
DBP	Diastolic Blood Pressure
DXA	Dual-energy X-ray absorptiometry
DiD	Difference in Differences
FMI	Fat Mass Index
HbA1c	Glycated haemoglobin
HCS	Healthy Conversation Skills
HeLTI	Healthy Life Trajectories Initiative
HIV	Human Immunodeficiency-virus
IQR	Interquartile Range
ITT	Intention-to-treat
MAR	Missing at Random
MCAR	Missing Completely At Random
MI	Multiple Imputation
NCD	Non-communicable disease
OWO	Overweight / Obesity
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SD	Standard Deviation
SBP	Systolic Blood Pressure

2 Abstract

The HeLTI South Africa trial is a Phase II randomised controlled trial evaluating the cumulative effect of a complex, multicomponent intervention, initiated preconception and continued through pregnancy and early childhood in Soweto, South Africa. The trial's primary endpoint is childhood adiposity at age 5 years, quantified as DXA-derived fat mass index (FMI; fat mass/height²), comparing offspring of women randomised to the intervention versus standard care. This Statistical Analysis Plan (SAP) documents the trial background and, specifically, prespecifies the analytic framework for Phase I (preconception). It defines analysis populations, outcomes, statistical models, handling of missing data, multiplicity, and details planned sensitivity and subgroup analyses for Phase I.

Keywords: Preconception health, multifaceted intervention, low- and middle-income setting, statistical analysis plan

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3 Administrative information

3.1 Study identifiers

Bukhali has ethical approval from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg, South Africa (main trial: M1811111 / process evaluation: M190449), Sinai Health System, Toronto, Canada (19-0066-E), and the World Health Organization Ethics Committee (ERC.0003328). This trial is also registered with the Pan African Clinical Trials Registry (https://pactr.samrc.ac.za); identifier: PACTR201903750173871.

3.2 Revision history

Version	Date	Details
1 (final)	April 2022	Overall RCT protocol published in BMJ Open: Norris SA, et al., Lye S. Building knowledge, optimising physical and mental health and setting up healthier life trajectories in South African women (*Bukhali*): a preconception randomised control trial part of the Healthy Life Trajectories Initiative (HeLTI). BMJ Open. 2022 Apr 21;12(4):e059914.
2.0 (draft)	September 2025	Full draft specifically specifying Phase I Statistical Analysis Plan of HeLTI SA trial
2.1 (final)	October 2025	Final signed off version

3.3 Contribution and approvals

See Appendix 1

4 Introduction

4.1 Synopsis

The Healthy Life Trajectories Initiative South Africa (HeLTI SA), locally known as *Bukhali*, is an individually randomised controlled trial designed to evaluate the cumulative effect of a complex, multicomponent intervention initiated in the preconception period and continued through pregnancy and early childhood. The trial aims to reduce childhood obesity – the primary outcome – and improve maternal health outcomes. Conducted in urban Soweto, South Africa, HeLTI SA recruited 7735 women, aged 18–28 years between October 2019 and December 2022 through community-based methods. Participants were randomly allocated (1:1) to an intervention or control arm. The intervention, delivered by trained "health helpers" comparable to community health workers, spans four phases (preconception, pregnancy, infancy, and early childhood) and includes health literacy materials, micronutrient supplementation, and structured behaviour change sessions using Healthy Conversation Skills (HCS). Women's body mass index (BMI), anaemia (haemoglobin), blood pressure, hyperglycaemia (HbA1c), human immunodeficiency virus (HIV) status, and mental health were also routinely monitored, with feedback and referrals provided as needed; at-risk women were able to consult a dietitian at least once per phase. The control group received monthly telephone-based life skills sessions alongside routine health care, HIV, and pregnancy testing. Participants were followed for up to 87 months – comprising a maximum of 18 months preconception, pregnancy, and 60 months of early childhood follow-up.

4.2 Study population

4.2.1 Inclusion criteria

- Women, aged 18-28 years, of African descent living in Soweto.
- Women who are willing to participate in the trial, provided informed consent, and are biologically capable of becoming pregnant during the preconception phase.

4.2.2 Exclusion criteria

- Women who reported a previous diagnosis of cancer, type I diabetes mellitus, or epilepsy; were currently pregnant at the time of screening (for preconception phase entry); or planned to relocate from Soweto within 12 months, were excluded.

4.3 Interventions

Intervention: The behaviour change intervention was developed using the taxonomy of behaviour change techniques and informed by three theoretical frameworks: (1) the theory of planned behaviour, which posits that behaviour is influenced by attitudes, perceived norms, and perceived behavioural control; (2) control theory, which focuses on the use of internal and external feedback mechanisms to reduce discrepancies between current and desired behaviours; and (3) social cognitive theory, which emphasises the interaction between personal factors, environmental influences, and goal-setting in shaping behaviour. Together, these frameworks ground the intervention in an understanding of context, individual needs, and supportive structures that enhance participants' sense of agency and capacity for change.

Participants therefore received a comprehensive intervention package delivered by trained "health helpers" (comparable to community health workers), comprising the following components (**Figure 1**):

1. **Health Literacy Resources** – Phase-specific educational materials covering nutrition, physical activity, mental health, and child development. Materials are provided as three resources during the preconception phase, one during pregnancy, and one during early childhood.
2. **Micronutrient Supplementation** – Multi-micronutrient supplements tailored to each phase, administered monthly throughout all phases.
3. **Healthy Conversation Skills (HCS) Sessions** – In-person and telephonic sessions using an empowerment-based behaviour change approach grounded in social cognitive theory, the theory of planned behaviour, and control theory, incorporating SMARTER goal-setting tools. Session frequency is three in-person plus nine telephonic during preconception, two in-person plus three telephonic during pregnancy, and ten in-person plus twenty telephonic during early childhood.
4. **Health monitoring and feedback** – Six key health areas are actively monitored, with feedback and referrals provided as needed: BMI, haemoglobin for anaemia, blood pressure, HbA1c for hyperglycaemia, HIV status, and mental health (including depression screening).
5. **Dietitian access** – Participants identified as at-risk received at least one consultation with a dietitian per phase.

Trial phase	Intervention component				
Intervention	**Health literacy resources (*n*, books)**	**Multi-micronutrient supplement (*n*, monthly doses)**	**In-person session and health feedback (*n*, sessions)**	**Telephonic contact (*n*, contact points)**	**Dietitian (for at-risk participants) (*n*, sessions)**
Preconception (18 months)	3	18	3	9	1
Pregnancy (9 months)	1	5	2	3	1
Early childhood (60 months)	1	6	10	20	1
Control			**In-person session (life skills), services offered (*n*, sessions)**	**Telephonic contact (life skills) (*n*, contact points)**	
Preconception (18 months)			3	9	
Pregnancy (9 months)			1	3	
Early childhood (60 months)			10	20	

Figure 1. Overview of the intervention components and dose for HeLTI SA arms (adapted from protocol).

Control: Participants in the control group received a monthly telephone-based life skills curriculum, access to standard health care, HIV testing, and pregnancy testing, but do not receive health literacy resources, micronutrient supplements, or HCS sessions.

4.4 Study visits

Table 1. Longitudinal data collection timeline (adapted from protocol).

	Preconception		Pregnancy (weeks)		Postpartum period (months)				
	Baseline	**18mnth**	**10-17**	**24-28**	**Delivery**	**6**	**12**	**24**	**60**
Demography									
Demographic and socioeconomic data, household composition, occupation, education, living environment	M	M	M	F		M	M	M	M
Date of birth/sex	M			F	C				
Anthropometry and body composition									
Height/length	M			F	C	C	C	C	C
Weight	M	M	M	M/F	C	M/C	M/C	M/C	M/C
Gestational weight gain			M	M					
Body mass index	M	M	M	M/F		M	M	M	M
Adiposity: DXA (adult)	M	M		F		M		M/C	M/C
Skinfolds (triceps and subscapular) (*if scan is not possible)			M	M		M*		M*	M*
Peapod body composition					C	C			
Waist circumference	M	M		F		C	M/C	M/C	M/C
Fetal anthropometry (gestational age and fetal growth)			C	C	C (GA)				
Mid upper arm circumference	M	M	M	M/F	C	C	C	M/C	M/C
Head circumference					C	C	C	C	C
Clinical									
Pregnancy complications			M	M					
Birth complications, survival					M/C	C	C	C	C
APGAR score 1 and 5 mins					C				
HIV test			M	F					M
Pregnancy test (pre-DXA scan)	M	M				M		M	M
Blood pressure	M	M	M	M/F			M	M/C	M/C
Anaemia (HemoCue)	M	M	M	M/F			M	M	M
HbA1c	M	M	M	M/F			M	M	M
Random blood glucose	M	M	M	F					
Fasting blood glucose				M			M	M/C	M/C
Oral glucose tolerance test				M					M/C
Plasma and serum collection	M	M	M	M/F			M	M/C	M/C
DNA collection	M	M	M	M/F			M		M/C
Urine spot sample	M	M		M/F				C	M/C
Urine dipstick	M	M	M	M/F				C	M/C
Heel-prick blood								C	

Buccal swab								C	
Lifestyle and health behaviour									
Diet intake (Dietary Diversity and Household Food Insecurity Access Scale)	M	M	M	M/F			M	M	M
Breastfeeding Questionnaire					M				
Feeding (breast feeding, solid food introduction, diversity, eating behaviour; SUNRISE Questionnaire)						C	C	C	C
Physical activity (M:GPAQ and Sitting Time Questionnaire)	M	M	M	M/F			M/C	M	M
Step test		M		F					
Accelerometry (substudy)								C	C
Screen Time Questionnaire	M	M	M	M/F		C	C	C	C
Sleep: Pittsburgh Sleep Quality Index	M	M	M	M/F		M	M	M	M
Brief Infant Sleep Questionnaire						C	C	C	
SUNRISE sleep questionnaire									C
Tobacco, alcohol, and drug use: Exposure questionnaire (WHO-STEPS, AUDIT-Questionnaire)	M	M	M	M/F			M	M	M
Environmental tobacco exposure				M			C	C	C
Child Care Questionnaire						M	M	M	M
Mental and physical health, and child development									
Depression (PHQ9)	M	M	M	M/F			M		M
Depression (Edinburgh)			M	M	M				
Stress (PSS)			M	M/F		M		M	M
Stressful life events (ACEs)	M			F					
Generalised Self-Efficacy Scale	M	M	M	M/F			M		M
Social Support Questionnaire	M	M	M	M/F					
Social Provisions Scale				M					M
Medical history (and TB), family history, drug, supplement history	M	M	M	M/F		M	M	M	M
Breastfeeding efficacy				M					
Anxiety (GAD-7)	M	M	M	M/F			M	M	M
Medication/supplement use	M	M	M	M/F	M/C	M/C	M/C	M/C	M/C
Medical events (hospitalisation)				M	M/C	M/C	M/C	M/C	M/C
Births, pregnancy and reproductive health	M		M		M	M	M	M	M
Vaccinations					C	C	C	C	C
Emotional health Questionnaire	M	M	M	M/F					
Ages and Stages Questionnaire					C	C	C	C	C
Parenting practices (Brigance Parent–Child Interaction Scale)							M	M	
Neurodevelopment (WHO Global Scale for Early Development—short-form)							C	C	
Executive function (Early Years Toolbox)									C

Temperament/behaviour (Strengths and Difficulties Questionnaire)	C	C
School readiness (International Development and Early Learning Assessment)		C
Stimulation in the home (UNICEF Multiple Indicators Cluster Survey Early Childhood Development, Home Learning Environment)	C	C

ACE, Adverse Childhood Events; C, infant/child; DXA, dual-energy X-ray absorptiometry; F, father; M, mother

Table 2. Longitudinal biological sample collection timeline (adapted from protocol).

	Preconception		**Pregnancy (weeks)**		**Postnatal period (months)**		
	Baseline	**18mnth**	**10-17**	**24-28**	**12**	**24**	**60**
Mother							
Blood collection	X (random)	X (random)	X (random)	X (fasting OGTT)	X (random)	X (random)	X (fasting OGTT)
Plasma	X	X	X	X	X	X	X
Serum	X	X	X	X	X	X	X
DNA	X		X	X	X		X
Urine (spot sample)	X	X		X			X
Urine (dipstick)	X	X	X	X			X
Father							
Blood-random				X			
Plasma				X			
Serum				X			
DNA				X			
Urine (spot sample)				X			
Urine (dipstick)				X			
Infant/child							
Blood collection (DBS)					X		
Blood collection						X (fasting)	X (fasting OGTT)
Plasma						X	X
Serum						X	X
DNA							X
Buccal swab						X	
Urine (spot sample and dipstick)						X	X

DBS, Dried Blood Spot; OGTT, Oral Glucose Tolerance Test

4.5 Outcomes

4.5.1 Primary outcomes

The primary outcome is childhood adiposity at age 5 years, measured by dual-energy X-ray absorptiometry (DXA)-derived fat mass index (FMI; fat mass/height²), comparing children of women in the intervention arm with those in the control arm receiving standard care.

4.5.2 Secondary outcomes

The study incorporates a comprehensive set of assessments to monitor maternal and child growth and development, alongside the collection of biospecimens to support research into the developmental origins of health and disease.

The effects of the 4-phase intervention on children at age 5 years will also be assessed across multiple domains:

- **Anthropometry**: Age- and sex-standardised BMI z-scores, BMI growth trajectories, Overweight/obesity (OWO), waist circumference z-score, upper arm circumference, and head circumference.
- **Cardiometabolic**: Systolic blood pressure (SBP) and diastolic blood pressure (DBP), lipid profile, glucose, insulin, and insulin resistance.
- **Behaviour**: Dietary intake, physical activity, screen time, sedentary behaviour, and sleep duration.
- **Developmental**: Cognitive, motor, communication, and behavioural measures.

The intervention's effects on maternal outcomes will be assessed across anthropometric, nutritional, physical, mental health, and behavioural domains:

- **Anthropometry**: Overweight/obesity (OWO), DXA-derived body composition, and waist circumference.
- **Nutrition**: Anaemia status.
- **Physical health**: Hypertension.
- **Mental health**: Depressive symptoms and anxiety.
- **Behaviour**: Dietary patterns, physical activity, screen time, sedentary behaviour, sleep duration, and tobacco and alcohol use.

4.5.3 Safety outcomes

- Any Serious Adverse Events during study period including:
    - Maternal adverse events during pregnancy and postpartum
    - Congenital anomalies
    - Childhood adversity
    - Mortality

4.6 Randomisation and blinding

4.7 Randomisation: Participants are individually randomised 1:1 using a computer-generated sequence with variable block sizes to preserve allocation concealment. An independent statistician, not involved in trial operations, oversees the randomisation. Allocation is concealed via a central, secure web-based system and is released only after eligibility is confirmed and baseline assessments are complete**.**

4.8 Blinding: Investigators and the research data-collection team are blinded to group assignment, which remains securely locked and inaccessible. The data management team may unblind a participant only at the request of the Data Monitoring Committee or the ethics committee for safety or mandated reporting. Blinding is maintained by (i) restricting database permissions, (ii) training staff and participants to avoid revealing allocation, and (iii) conducting intervention and control activities in separate areas.

4.9 Sample size

The sample size estimation is based on a mean FMI of 4.1 kg/m² and a standard deviation (SD) of 2.1, derived from DXA data from prepubertal children in the Birth to Twenty Plus Cohort in Soweto, South Africa. To detect a clinically meaningful difference of 0.25 SD (equivalent to 0.5 kg/m²) in FMI at age 5 years between the intervention and control groups, with 80% power and a 5% significance level, 765 children per arm are required. Allowing for an estimated 30% attrition rate, approximately 6800 women will need to be recruited to achieve a target of 1530 pregnancies.

5 Statistical analysis

5.1 Statistical hypotheses

The primary statistical hypotheses are as follows:

- **Null hypothesis (H_0):** The integrated, multi-phase intervention delivered from preconception through pregnancy, infancy, and childhood has no effect on childhood adiposity, risk for non-communicable diseases (NCDs), or developmental outcomes at age 5 years compared with standard care plus.
- **Alternative hypothesis (H_1)**: The integrated, multi-phase intervention delivered from preconception through pregnancy, infancy, and childhood reduces childhood adiposity and risk for NCDs and improves child developmental outcomes at age 5 years compared with standard care plus.

Secondary hypotheses:

- The trial also tests multiple secondary hypotheses relating to maternal health outcomes, birth outcomes, and child development outcomes, as detailed in Section 4.5.2.

5.2 Statistical principles

5.2.1 Level of statistical significance

All hypothesis tests will be two-sided with a nominal α=0.05. The final analysis will retain a 5% significance threshold. To address multiplicity, the false positive rate will be controlled at 5%; subgroup and sensitivity analyses will be treated as exploratory (no multiplicity adjustment), with interpretation guided primarily by treatment-by-subgroup interaction p-values.

5.2.2 Statistical software

Analyses will be conducted primarily using STATA, or R (version R 4.3.1 or above).

5.3 Phased unblinding approach

Given the HeLTI consortium's unique design - comprising four harmonised, individually powered trials conducted over a 10+ year period across four countries - it is neither feasible nor appropriate to maintain full blinding until the final primary outcome analysis.The decision to adopt a phased unblinding and analysis strategy emerged through a structured and transparent deliberative process led by the HeLTI Research Committee (RC) and facilitated by the World Health Organisation Secretariat. Recognising the unique scale, duration, and complexity of the HeLTI initiative, the consortium acknowledged early on that the traditional model of maintaining full blinding until the final primary outcome was impractical and potentially detrimental to scientific and operational progress.

At the first HeLTI Data Management Workshop (September 2017), the RC and WHO Secretariat agreed on a systematic approach to resolve this methodological dilemma. The process entailed:

1. **Formal articulation of the problem** in writing, outlining the ethical, logistical, and scientific challenges associated with full blinding in a long-term, multicomponent public health intervention.
2. **Engagement of a panel of international experts**, including trialists, bioethicists, statisticians, and funder representatives, to provide input within their respective domains.
3. **Review and synthesis of expert inputs** during the June 2018 RC meeting to evaluate the implications of various unblinding scenarios.
4. **Consensus building** within the RC, culminating in an agreed position supporting phased unblinding at the end of each intervention phase—preconception, pregnancy, infancy, and early childhood.
5. **Consideration of knowledge dissemination**, with the recommendation to document and publish the process and rationale as a methodological contribution to complex, life-course intervention research.
6. **Formal endorsement** of the agreed position by the HeLTI Council of funders
7. **Ongoing oversight** by the RC, with facilitation and coordination by the WHO Secretariat to ensure adherence to agreed principles across all HeLTI trials.

This structured, multi-stage decision-making process ensured transparency, accountability, and alignment with international best practice. It also allowed the consortium to balance scientific rigour, ethical responsibility, and pragmatic trial management. The resulting phased approach enables interim publication of phase-specific outcomes once all participants have completed that stage, without compromising the integrity of the overall trial or its primary endpoints

5.4 Phase I Statistical Analysis Plan

5.4.1 Definition: Phase I for HeLTI SA RCT is defined as the phase examining the effect of the intervention on women's health who completed a minimum 18-month period without becoming pregnancy)

5.4.2 Hypothesis:

- The intervention will reduce the risk of clinical (obesity, hypertension, diabetes, depression) and nutritional (anaemia) outcomes of interest

5.4.3 Concise methods overview

- **Design & analysis populations:** Parallel-arm RCT; analyses conducted primarily under the intention-to-treat (all randomized participants). Per-protocol and as-treated analyses will be reported as sensitivity analyses with protocol-defined adherence criteria.
- **Estimand framework:** For each Phase I outcome, the primary estimand is the mean difference (or proportional difference) between intervention assignment versus control at the prespecified assessment time (exit post minimum 18months of the intervention) regardless of post-randomization adherence (ITT, treatment-policy strategy).
- **Outcomes of interest (Phase I):** Prespecified preconception outcomes will be analysed as detailed in the SAP. Continuous outcomes analysed on their native or appropriately transformed scales; binary outcomes via risk difference and risk ratio.
- **Models:**
  - Continuous outcomes: ANCOVA (outcome at assessment regressed on treatment arm, baseline value of the outcome when available, and prespecified covariates); all regression analyses will use heteroskedasticity-consistent (HC3) robust standard errors to account for potential variance heterogeneity and improve the reliability of statistical inference. The HC3 estimator is selected ensuring valid confidence intervals and hypothesis tests under potential heteroskedasticity and minor model misspecification.
  - Binary outcomes: log-binomial regression (or Poisson with robust variance if non-convergence).
- **Covariate adjustment (prespecified):** age, baseline measure (if applicable), HIV status (note: consider sensitivity analyses including and excluding participants living with HIV where HIV and treatment maybe highly associated with outcome of interest).
- **Missing data:** Multiple imputation by chained equations under missing-at-random, including treatment arm, baseline predictors, and auxiliary variables; number of imputations ≥ fraction of missing information×100 (min 20). Sensitivity analyses: complete-case, and δ-adjusted MNAR tipping-point analyses for key outcomes.

- **Multiplicity:** For Phase I, outcomes of interest, treat each condition as a family (obesity, hypertension, diabetes, depression, anaemia). Control within-family multiplicity using Holm (FWER 5%). Subgroup and sensitivity analyses are exploratory (no adjustment). Within each family, we will control the [FWER using Holm at α=0.05 | FDR using Benjamini–Hochberg at q=0.05]. Subgroup analyses will be interpreted via treatment-by-subgroup interaction tests; within-subgroup effect estimates are exploratory. Sensitivity analyses are presented for robustness and are not multiplicity-adjusted. Family-wise control within outcome domains using Holm or false discovery rate (Benjamini–Hochberg) as specified; the Phase I confirmatory endpoint (if designated) tested two-sided at α=0.05. All other Phase I endpoints treated as secondary/exploratory with adjusted CIs where applicable.
- **Subgroups (prespecified, interaction-tested):** Baseline BMI category, parity, HIV status. Treatment-by-subgroup interaction terms will be assessed; subgroup estimates presented with interaction p-values.
- **Sensitivity analyses:**
    - Per-protocol effect among adherent participants.
    - CACE (complier average causal effect) using randomisation as an instrument where adherence is well-defined.
    - Alternative model specifications (e.g., robust regression, transformation-free methods) and influence diagnostics.
- **Interim analyses & stopping:** None planned for efficacy in Phase I; data quality checks only.
- **Presentation:** show adjusted risk ratios (or common odds ratios for ordinal), risk differences (marginal standardisation), and adjusted mean differences for continuous outcomes. Provide arm-specific adjusted probabilities/means.
- **In future we will explore conditional average treatment effects (CATE) for potential treatment heterogeneity.**

5.4.4 Outcomes of interest

- Diabetes – HbAIc, glucose fasting, 1-hr, and 2-hr & classification (by HbA1c or OGTT)
- Hypertension – SBP; DBP; MAP & classification
- Obesity – BMI & classification
- Anaemia – Hb & classification
- Depression – classification
- Composite: Metabolic syndrome; PREVENT

5.4.5 Ancillary outcomes of interest

- Lipids – total, LDL, HDL, Triglycerides & classification
- DXA-derived body composition
    - Whole-Body Adiposity: Fat mass, Fat mass index
    - Central Adiposity: VAT, SAT, Android fat, Gynoid fat
    - Peripheral Adiposity: Trunk fat % of fat mass, Arm fat % of fat mass, Leg fat % of fat mass
    - Lean Mass/Soft Tissue: Lean mass; Lean mass index; Fat-free soft tissue mass
- Central adiposity - waist circumference & classification

- Self-efficacy - classification
- Anxiety - classification
- Change in weight (adjusted for baseline weight)
- On treatment (hypertension, diabetes depression)
- Cardiovascular health risk indicators
- Suicidal ideation
- Contraceptive use – reproductive agency
- Inflammation (for example: hsCRP & inflammatory load)

Obesity

a) BMI (continuous)

- **Model:** ANCOVA: BMI_exit ~ arm + BMI baseline + covariates (HC3 SEs).
- **Estimand:** Adjusted mean difference (kg/m²).
- **Diagnostics:** Residual plots; if skewed, also report quantile regression (median difference).

b) BMI categories (4 levels; ordered)

- **Model: Ordinal logistic (proportional odds)** with arm + covariates.
- **Estimand: Common odds ratio** (higher category = greater adiposity).
- **Checks:** Test proportional-odds assumption (Brant/score tests).
    - If violated: **partial proportional-odds** or **multinomial logit** as sensitivity.
- **Alternative effect metric:** Marginal probabilities and **risk differences** by category.

Hypertension

a) SBP, DBP, MAP (continuous)

- **Model:** Separate ANCOVA for each: outcome exit ~ arm + outcome baseline + covariates (HC3).
- **Estimand:** Adjusted mean difference (mmHg).

b) Hypertension status (3 levels ordered; e.g., normotensive / pre- / hypertensive)

- **Model:** Ordinal logistic (or multinomial if non-proportional).
- **Estimand:** Common OR (ordered worsening). Provide marginal category risks.

Diabetes

a) Glucose fasting, 1hr, 2hr HbA1c (continuous)

- **Model:** Separate ANCOVA for each: outcome exit ~ arm + outcome baseline (if applicable) + covariates (HC3).
- **Estimand:** Adjusted mean difference (mmol/l; %).

b) Diabetes status (2 categories)

- **Model: Log-binomial regression** for **risk ratio** (preferred).
    - Fallback: **Poisson with robust variance** if log-binomial fails to converge.
- **Covariates:** Include baseline glycaemia if available (e.g., HbA1c/FG) or baseline diabetes status.
- **Estimands:** Risk ratio (primary) and risk difference (marginal standardisation).
- **Optional continuous markers (if available):** ANCOVA for HbA1c/FG.

Depression

a) Depression severity (2 and 3 categories; ordered)

- **Model:** Ordinal logistic with arm + covariates (including baseline score/severity).
- **Estimand:** Common OR (worse category = higher severity).
- **Sensitivity:** If proportional-odds violated, partial-PO or multinomial.

Anaemia

a) Haemoglobin (continuous)

- **Model:** ANCOVA: Hb exit ~ arm + Hb_baseline + covariates (HC3).
- **Estimand:** Adjusted mean difference (g/dL).

b) Anaemia categories (3 levels; ordered)

- **Model:** Ordinal logistic; report common OR and marginal probabilities.
- **Sensitivity:** Partial-PO / multinomial if assumption fails.

Subgroups (pre-specified, interaction-tested)

- Baseline BMI class, HIV status & parity.
- **Model:** Add arm×subgroup interaction to the primary model for each outcome.

- **Interpretation:** Emphasise **interaction p-values**; within-subgroup estimates are exploratory.

Robustness/sensitivity across outcomes

- **Model-free check:** In addition to parametric models, provide **non-parametric** contrasts (e.g., Hodges–Lehmann median differences for continuous outcomes).
- **Influence/fit:** Leverage and influence diagnostics; compare HC3 vs HC0/HC1 SEs (expect similar conclusions).

Reporting template (example)

At exit, the adjusted mean difference in BMI between intervention and control was Δ=…, 95% CI …; HC3 SEs; n=…. The common OR for shifting to a higher BMI category was … (95% CI …), proportional-odds assumption p=…. Within the hypertension family, after Holm adjustment, the arm effect remained significant for SBP (adj-p=…), but not for DBP or MAP. Diabetes risk ratio was … (95% CI …), and depression severity common OR was … (95% CI …). For haemoglobin, the adjusted mean difference was … (95% CI …).”

Stata code (example BMI, hypertension)

```
* Covariates

global COVARS age index hiv


* 1) OBESITY

* a) BMI continuous (HC3 robust SEs)

regress bmi_e arm bmi_b $COVARS, vce(hc3)


* b) BMI categories (ordinal)

ologit bmi_cat_e arm $COVARS, vce(robust)

* Proportional-odds check (Brant test; user-written)


* 2) HYPERTENSION

* a) SBP / DBP / MAP continuous

regress sbp_e arm sbp_b $COVARS antihyp_e, vce(hc3)

regress dbp_e arm dbp_b $COVARS antihyp_e, vce(hc3)
```

```
regress map_e arm map_b $COVARS antihyp_e, vce(hc3)


* b) Hypertension category (ordinal)
ologit htn_cat_e arm $COVARS, vce(robust)
```

Model diagnostics and robustness

- **Linearity & residuals:** Partial residuals; check influential points (Cook's D), leverage; compare HC3 vs HC1 (expect similar inference).
- **Ordinal models:** Proportional-odds assumption (Brant/score tests; nominal test for clm)
- **Non-parametric checks:** Hodges–Lehmann median differences for continuous outcomes.

Suggested Tables/Figures (TLFs) examples

- **TLF-O1:** Adjusted mean differences (BMI, SBP, DBP, MAP, Hb) with 95% CIs.
- **TLF-O2:** Adjusted RRs/RDs (diabetes).
- **TLF-O3:** Ordinal common ORs with proportional-odds assumption tests (BMI cat, HTN cat, depression cat, anaemia cat).
- **TLF-O4:** Family-wise multiplicity-adjusted p-values (Holm) within each condition family.
- **TLF-O5:** Subgroup Forest plots for arm effects (interaction p-values).