

Effect of LNS supplementation on the depressive symptoms of Ghanaian women at 6 months post-partum

Statistical analysis plan (Addendum to iLiNS Dyad-G main SAP)

Prepared for:

The International Lipid-based Nutrient Supplements (iLiNS) Project, Ghana

Micronutrient supplementation during pregnancy and lactation and maternal depression at 6mo postpartum

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Authors	Harriet E.T. Okronipa Seth Adu-Afarwuah, PhD
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Version History Log

This table will detail the version history for this document. It will detail the key elements of the changes to the versions.

Version	Date implemented	Details of significant changes

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1.0 Introduction

The International Lipid-based Nutrient Supplements (iLiNS) Project is a multi-country (Ghana, United States, Finland, France, Malawi and Burkina Faso) research collaboration with the goal to expand the evidence base for the use of lipid-based nutrient supplements (LNS) for preventing malnutrition in vulnerable populations. The study in Ghana aims to determine the efficacy of LNS for pregnant and lactating women and their infants. This document describes the statistical analysis plan (SAP) for assessing the effect of LNS on maternal depressive symptoms at 6mo postpartum.

2.0 Study design

Pregnant women were recruited from antenatal clinics and randomly assigned to one of three intervention groups: (a) Daily iron and folic acid during pregnancy, and calcium (Ca) only (akin to a placebo) during the first 6 months postpartum; (b) Daily multiple micronutrients during pregnancy and the first 6 months postpartum, and (c) Daily LNS during pregnancy and the first 6 months postpartum (LNS-P&L with similar vitamin and mineral content as the daily multiple micronutrients, plus Ca, P, K, Mg and essential fatty acids).

3.0 Objective of analysis

To examine the effect of the intervention on maternal depression symptoms at 6mo postpartum

3.1 Specific hypothesis to be tested

1. Women who received LNS during pregnancy will have lower mean Edinburgh Postnatal Depression Scores (EPDS) scores at 6mo postpartum compared to women who received either IFA or MMN
2. The proportion of women who score ≥ 12 ¹ on the EPDS at 6 mo postpartum will be lower among women who received LNS during pregnancy than among women who received either IFA or MMN

4.0 Data collection

Background demographic information was collected at enrolment. Maternal depression symptoms were assessed at 6mo postpartum (and up to one month from scheduled date in case mother travelled) using the Edinburgh Postnatal Depression Scale, EPDS (Cox et al., 1987). The EPDS is a 10-item scale that documents depressive symptoms that occurred over the past 7-days. Each item on the scale was scored on a 4- point rating scale that represented the level of occurrence. The scores for all 10-items will be summed up to obtain a total depression score. Missing values will be imputed if more than 5 observations or individuals are missing on one or more items on the scale. Where 5 or less individuals are missing on one

¹ EPDS cut off of 12 has been validated among Zimbabwean and South African postpartum women (Chibanda et al., 2010, Lawrie, et al.1998).

or more items, the EPDS scores for those individuals will be considered as missing. Mothers with total scores below 12 will be classified as not showing symptoms of depression whereas those with total EPDS scores 12 and above will be classified as showing symptoms of depression (Chibanda et al., 2010, Lawrie, et al.1998).

5.0 Outcome variables

1. Total EPDS score at 6 months post-partum: This is a continuous variable and will be defined as the total score for all 10-items on the EPDS.
2. EPDS \geq 12: A cut off of ≥ 12 ² indicates symptoms of maternal depression. It is a dichotomous variable.

6.0 Software for analysis

All analysis will be done using SAS version 9.3 (SAS Inst. Cary, NC, USA).

7.0 Analysis principles

Analysis will be by intention-to-treat. Results for all women enrolled will be analyzed according to the group to which they were assigned regardless of adherence to treatment or any protocol violation. Data on subjects who were lost to follow-up (either temporarily or permanently) will be included in the analysis if available.

8.0 Study flowchart

A participant flow diagram (Figure 1) will be prepared in accordance with the CONSORT 2010 guidelines. The figure will include the numbers and reason for permanent loss to follow up between screening and the 6mo time point when maternal depression outcome was evaluated.

9.0 Data cleaning

The first round of data cleaning has been completed and involved a series of steps as follows;

1. At the field site, Data Monitors first checked all forms manually for completeness, consistency and correctness before the forms were sent to the Accra office for double entry.
1. At the Accra office, all forms entered by the two data entry clerks were verified by the data Manager and differences resolved by re-checking the original scanned form.
2. Special SAS syntax was then used to generate additional queries which were then forwarded to the field office and resolved.

² EPDS cut off of 12 has been validated among Zimbabwean and South African postpartum women (Chibanda et al., 2010, Lawrie, et al.1998).

A final round of data cleaning will be done before statistical analysis by re-running special SAS syntax. Generated queries will be investigated and corrected.

10.0 Data analysis

- i) All tests will be two-sided, at 5% level of significance, except otherwise stated
- ii) A set of pre-specified covariates (see below) will be examined. Only covariates significantly associated with the outcome at 10% level of significance in bivariate analysis will be included in the final adjusted analysis.
- iii) ANCOVA for the continuous outcome (normality will first be checked to see if they are normally distributed) or logistic regression for the dichotomous outcome will be used to test the null hypothesis of no difference among the three groups. We will first run the model without covariates, then run them again controlling for the pre-specified covariates.
- iv) Potential effect modifiers will be examined and their effect assessed with an interaction term in the ANCOVA or logistic regression model. When an interaction is found to be significant ($p < 0.1$), adjusted means (LSMEANS) will be estimated in order to further understand the nature of the effect modification.
- vii) If there are significant differences in the prevalence of EPDS ≥ 12 between groups, adjusted relative risks and 95% CI will be estimated using the method described by Spiegelman and Hertzmark (Spiegelman and Hertzmark, 2005).

11.0 Potential covariates and effect modifiers

Independent of the intervention, maternal depression could be affected by a variety of household, maternal, and infant factors. Each pre-specified covariate (listed below), will be examined for completeness of data, and a decision will be made for the exclusion of a covariate with a large number of missing data.

Similarly, most of the covariates listed below could interact with the intervention to influence maternal depression. In the examination of potential effect modifiers, each will be considered separately in the regression model to avoid colinearity. The table below shows the covariates and effect modifiers that will be examined:

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Covariates	Effect modifiers
Maternal years of formal education	Maternal years of formal education
Maternal anemia at enrolment	Maternal anemia at enrolment
Maternal BMI at enrolment	Maternal BMI at enrolment
Gestational age at enrolment	Gestational age at enrolment
Maternal height	Maternal height
Maternal age	Maternal age
Marital status	Marital status
Primiparity	Primiparity
Household Assets Index	Household Assets Index
Housing index	Housing index
Household food insecurity index	Household food insecurity index
Season at enrolment	Season at enrolment
Infant low birthweight	Infant low birthweight
Infant sex	Infant sex
[†] two different household food insecurity index variables will be examined, one 'as is' (i.e without adjustment for seasonality) and the other with adjustment for seasonality	

12.0 Baseline characteristics

Selected background characteristics (measured at baseline) will be examined by treatment group (Table 1)

13.0 Tables & Figures

Table 1: Baseline characteristics of women who completed the study by intervention group

Variable	IFA^a ($\bar{x} \pm SD$) [n]	MMN ($\bar{x} \pm SD$) [n]	LNS ($\bar{x} \pm SD$) [n]
Number of participants	x.x	x.x	x.x
Maternal age (y)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Maternal education (y)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Married or cohabiting (% [n])	x.x [xxx]	x.x [xxx]	x.x [xxx]
Maternal BMI (kg/m ²)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Maternal height (cm)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Mother's gestational age at enrolment (wk)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Iron deficiency anemia in pregnancy (% [n])	xx.x [xxx]	xx.x [xxx]	xx.x [xxx]
Parity (#)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Infant birth weight (kg)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Infant male sex (% [n])	x.x [xxx]	x.x [xxx]	x.x [xxx]
Household Assets Score (#)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Household Food Insecurity Score (#)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]
Household Housing Index (#)	x.x \pm x.x [x]	x.x \pm x.x [x]	x.x \pm x.x [x]

^aLNS=lipid-based nutrient supplement group; MMN=multiple micronutrient group; IFA=iron folic acid group (standard care)

Table 2: Maternal mean depression score by intervention group^a										
Variable	IFA mean (SD)	MMN mean (SD)	LNS mean (SD)	P- value	Compariso n of MMN and IFA		Comparison of LNS and IFA		Comparison of LNS and MMN	
					Difference in means (95%CI)	P- value	Difference in means (95%CI)	P- value	Difference in means (95%CI)	P-value
EPDS ² score at 6mo	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	x.x x	xx.x (x.x-x.x)	x.x x	xx.x (x.x-x.x)	x.x x	xx.x (x.x-x.x)	x.x x
EPDS score at 6mo (Adjusted model)	xx.x (x.xx)	xx.x (x.xx)	xx.x (x.xx)	x.x x	xx.x (x.x-x.x)	x.x x	xx.x (x.x-x.x)	x.x x	xx.x (x.x-x.x)	x.x x

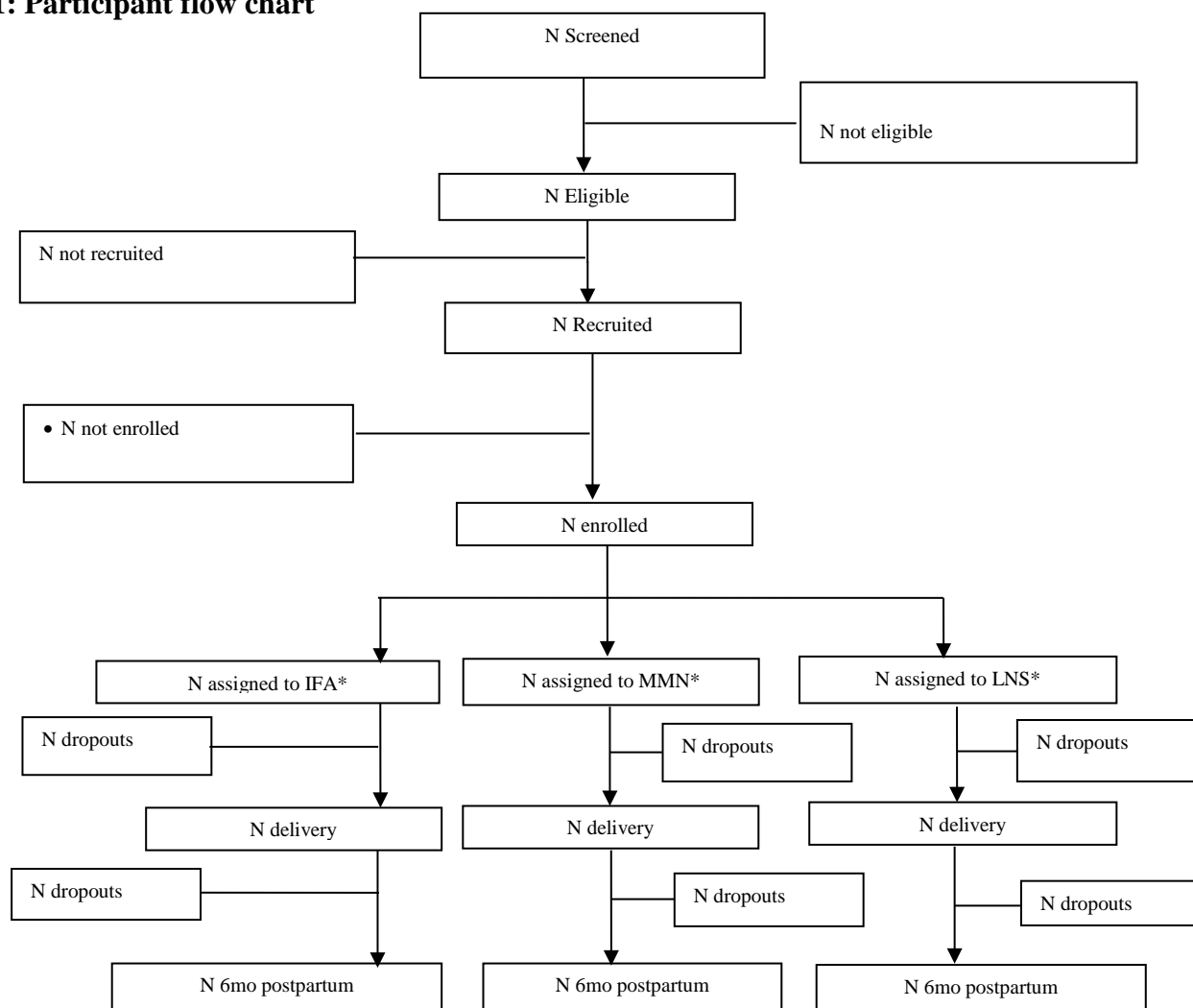
^aLNS=lipid-based nutrient supplement group; MMN=multiple micronutrient group; IFA=iron folic acid group (standard care)
EPDS=Edinburgh Postnatal Depression Scale.

Table 3: Prevalence of maternal depressive symptoms (EPDS ≥ 12)^a at 6mo by intervention group^b										
Variable	IFA n (/%)	MMN n (/%)	LNS n (/%)	P- value	Comparison of MMN and IFA		Comparison of LNS and IFA		Comparison of LNS and MMN	
					Risk ratio (95%CI)	P- value	Risk ratio (95%CI)	P- value	Risk ratio (95%CI)	P-value
Maternal depressive symptoms (Unadjusted Risk Ratio)	x.x (x.x%)	x.x (x.x%)	x.x (x.x%)	x.x x	x.x (x.x-x.x)	x.x x	x.x (x.x-x.x)	x.x x	x.x (x.x-x.x)	x.x x
Maternal depressive symptoms Adjusted Risk Ratio (95%CI)				x.x x	x.x (x.x-x.x)	x.x x	x.x (x.x-x.x)	x.x x	x.x (x.x-x.x)	x.x x

^aEPDS=Edinburgh Postnatal Depression Scale. Cut off of 12 has been validated among Zimbabwean and South African postpartum women (Chibanda et al., 2010, Lawrie, et al.1998).

^bLNS=lipid-based nutrient supplement group; MMN=multiple micronutrient group;.IFA=iron folic acid group (standard care)

Figure 1: Participant flow chart



* IFA= Iron-Folic Acid capsules; MMN=Multiple Micronutrient capsules; LNS=Lipid-based nutrient supplement for pregnant and lactating women.

14.0 References

1. Chibanda, D., et al., Validation of the Edinburgh Postnatal Depression Scale among women in a high HIV prevalence area in urban Zimbabwe. *Archives of Women's Mental Health*, 2010. **13**(3): p. 201-206.
2. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10 item Edinburgh Postnatal Depression Scale. *Br J Psychiatry*. 1987;150(6):782–6.
3. Lawrie, T.A., et al., Validation of the Edinburgh Postnatal Depression Scale on a cohort of South African women. *S Afr Med J*. 1998 Oct;88(10):1340-4.
4. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol* 2005;162(3):199-200. doi: 10.1093/aje/kwi188.