# Efficacy of lipid-based nutrient supplements (LNS) for pregnant and lactating women and their infants

## Statistical analysis plan

Prepared for**:**

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

## Table of contents

| | |
|---|---|
| Version number | 1 |
| Version date | Feb 20, 2013 |
| Authors | Seth Adu-Afarwuah, PhD<br>Janet M. Peerson<br>Mary Arimond |
| Implementation date of current version | Feb 20, 2013 |

| | | |
|---|---|---|
| Approved by | Name/Position | Anna Lartey, PhD/ PI |
| | Signature | *Signature withheld from internet version* |
| | Date | Feb 20, 2013 |
| | | |
| | Name/Position | Kathryn G. Dewey, PhD/ PI |
| | Signature | *Signature withheld from internet version* |
| | Date | Feb 20, 2013 |
| | | |
| | Name/Position | Per Ashorn, MD, PhD/PI |
| | Signature | *Signature withheld from internet version* |
| | Date | Feb 20, 2013 |
| | | |

**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 |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

## 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. In Ghana the iLiNS Project focuses on the efficacy of LNS for pregnant and lactating women and their infants, and is referred to as iLiNS DYAD-G. Primary data collection began in December 2009. Below we describe the iLiNS DYAD-G's statistical analysis plan whilst data collection is still ongoing, before any knowledge of the study results. Data collection is expected to be completed by end of 2013.

## 2.0 Overview of study

### 2.1 Title

The iLiNS DYAD-G study is a randomized, partially double blind, controlled trial that compares three micronutrient treatments, and targets women during pregnancy (from $\leq$ 20 gestational weeks to delivery) and the first six months postpartum, and their offspring during infancy (from birth to 18 mo of age). The treatments are: (a) Daily iron and folic acid during pregnancy, and calcium (Ca) only (akin to a placebo) during the first 6 months postpartum, with no supplementation for offspring during infancy; (b) Daily multiple micronutrients (1-2 RDA of 18 vitamins and minerals) during pregnancy and the first 6 months postpartum, with no supplementation for offspring during infancy, 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), with LNS for offspring (LNS-20gM with 22 vitamins and minerals with concentrations based on RNIs for infants) during infancy.

### 2.2 Study population

We screened (by means of a questionnaire) pregnant women attending usual ante-natal clinics who were at least 18 years of age and were no more than 20 weeks pregnant (based on either fundal height measurement or ultrasound), and excluded those who refused the screening, or were more than 20 weeks pregnant or less than 18 years of age. Women who passed the screening and later gave consent to participate in the study were considered r***ecruited***, but not yet enrolled. *Recruited* women who attended baseline laboratory and anthropometric assessments, and were randomized into one of the three treatment study groups were considered ***enrolled***. Only *enrolled* women were considered full participants of the study.

In terms of pregnant women's ages, there was no upper limit for inclusion into the study, and in terms of gestational age, there was no lower limit. All singleton offspring of the pregnant women became part of the study, but when a woman gave birth to more than one infant, only one was randomly selected for inclusion in the study.

### 2.3 Inclusion criteria

#### 2.3.1 Inclusion criteria (pregnant women)

Pregnant women were eligible for inclusion in the study if all of the following criteria were met:

a) At least 18 years of age

b) No more than 20 wk of gestation (as determined by fundal height measurement or ultrasound scan) at the time of enrolment.
c) Prepared to sign an informed consent
d) Participated in baseline anthropometric and laboratory assessment.

#### 2.3.1 Inclusion criteria (infants)

Infants were eligible for the study if they were delivered from the pregnancy for which their mothers were enrolled into the study.

## 2.4 Exclusion criteria

#### 2.4.1 Exclusion criteria (pregnant women)

Pregnant women were excluded from the study if one or more of the following criteria were present:

a) HIV positive (as from the Ante-natal card).
b) Known to be allergic to milk or peanut.
c) Presence of asthma, epilepsy, tuberculosis or any other chronic disease (e.g. malignancy) requiring frequent medical attention (as from the Ante-natal card).
d) Not residing in the study site (defined by the area between the southern end of Somanya and the northern end of Kpong, along the Somanya-Kpong trunk road in the Manya Krobo and Yilo Krobo districts).
e) Intention to move from the study site.
f) Unwilling to receive into the home the study's field workers who would deliver study supplements and administer questionnaires.
g) Already participating in a clinical trial.
h) Unwilling to take study supplement.

#### 2.4.2 Exclusion criteria (offspring)

An infant was excluded from the study if the infant's mother had multiple births (more than one child from the pregnancy) and the infant was not randomly selected for inclusion into the study.

## 2.5 Objectives

The primary aim of the study is to compare the effects of three types of micronutrient supplements among Ghanaian pregnant and lactating women and to assess the effect of LNS-P&L given to pregnant and lactating women and LNS-20gM provided to children from 6 to 18 mo of age on child growth and micronutrient status. We also aimed to explore what background characteristics (e.g. social, economic, demographic, health, nutritional, etc.) might modify the effects of LNS among women and their infants.

The null hypotheses were that:

a) The three groups of infants whose mothers receive the three micronutrient treatments will not differ significantly in mean birth length (crude length and length-for-age z-score), and

b) Infants whose mothers received LNS during pregnancy and lactation, and who receive LNS from 6 to 18 months of age will not differ significantly in length-for-age z-score at 18 mo from infants of the other two groups.

**2.6 Blinding**

The statistical analysis plan was written by study investigators, all of whom were blinded to the group assignments, until the final study results are released by the study statistician.

**2.7 Efficacy outcomes**

**2.7.1 Primary efficacy outcomes**

The study has two primary efficacy outcomes, namely:

a) Length of baby delivered by enrolled woman measured within 48 hours of delivery, which is defined by (i) Crude length in cm, and (b) Length-for-age z-score, and
b) Length-for-age z-score of child at 18 mo of age.

**2.7.2 Secondary efficacy outcomes**

Secondary outcomes include:

*Maternal:*

- Anthropometric status (weight, BMI, mid upper arm circumference and sub-scapular skin-fold thickness) at 36 gestational weeks (GW) and 6 mo postpartum.
- Weight of child delivered (measured within 48 hours of delivery).
- Gestational age at delivery.
- Anemia, micronutrient (iron, vitamin A, B-vitamins, zinc) and essential fatty acid status at 36 GW and 6 mo postpartum.
- Malarial antigen at 36 GW and 6 mo postpartum.
- Total plasma cholesterol at 36 GW.
- Blood pressure and urinary iodine, isoprostane (marker of oxidative stress) and 8-hydroxy-2'deoxyguanosine (8-OHdG) (marker of DNA damage) at 36 GW.
- Breast milk composition (essential fatty acids, vitamin A, B-vitamins, iodine) at 6 mo postpartum.
- Depressive symptoms at 6 mo postpartum.
- Salivary cortisol at 28 GW and 36 GW**.**
- Morbidity between enrollment and 36 GA and 6 mo post-partum.

*Child:*

- Anthropometric status (weight, length, head circumference and mid upper arm circumference) at birth and 3, 6, 12 and 18 mo.
- Anemia, micronutrient (iron, vitamin A, B-vitamins, iodine) and essential fatty acid status, and malarial antigen at 6 and 18 mo.
- Morbidity between 6 and 18 mo.
- Child feeding practices and maternal report of child sleep patterns at 6, 12 and 18 mo.
- Energy and nutrient intake from complementary foods at 9 and 15 mo.
- Antibody response to measles vaccination at 12 mo.

- Achievement of five motor milestones (sitting without support, standing alone, walking with assistance, walking alone and running) and four other developmental milestones (pronouncing single words like mama / dada, waving goodbye, eating by self, drinking from a cup) from 0 to 18 mo of age.
- Neuro-behavioral development at 18 mo of age.

### 2.8 Safety outcomes

We assessed safety by evaluating (a) Adverse events (b) Severe adverse events, and (c) Abnormally low anthropometric values.

#### 2.8.1 Adverse events

**i. Women**

Adverse events outcomes were:

a) Proportion of follow-up visits completed at which woman reported adverse event since last visit/during last two weeks.
b) Proportion of days under surveillance woman had adverse event.
c) Proportion of follow up visits completed at which woman reported adverse event on the day preceding the visit day.
d) Number of visits to a clinic, hospital or pharmacy because of morbidity symptoms

Adverse events included the presence of the following at any follow up visit:

- Loss of appetite
- Nausea
- Vomiting
- Diarrhea
- Bloody stools
- Mucus in stool
- Fever
- Mastitis (during lactation only)
- Cough
- Sore throat
- Nasal discharge
- Pregnancy related abdominal pain (during pregnancy only)
- Pregnancy related bleeding (during pregnancy only)
- Visit to clinic, hospital or pharmacy because of morbidity symptoms

**ii. Infants**

Adverse events outcomes were:

a) Incidence of mild, moderate and severe morbidity symptoms.
b) Number of visits to a clinic, hospital or pharmacy because of morbidity symptoms.
c) Prevalence of morbidity at 6, 12 and 18 months.

Morbidity definitions will be based on the following symptoms assessed:

- Rashes
- Reduced activity due to illness

- Poor appetite
- Poor stool consistency (semi-liquid, liquid or very liquid)
- Blood or mucus in stool pathology
- Vomiting
- Fever
- Cough
- Rapid breathing
- Difficult breathing
- Nasal discharge

**2.8.2 Serious adverse events**

Serious adverse events (SAE) outcomes:

a) Number of SAEs reported, ie. if a subject has more than one occurrence of SAEs, all the SAEs will be counted.
b) Number and proportion of subjects with SAEs i.e. if a subject has more than one occurrence of SAEs, the subject will be counted only once.

Conditions regarded as SAEs were:

a. Death of subject.
b. Any loss of pregnancy regardless of gestational age.
c. Hospitalization (overnight stay in the hospital because of illness).
d. Hemoglobin less than 5.0 g/dl (or 50 g/l).
e. Subject extremely ill. This is used to define (**a**) "l**ife-threatening conditions**" (including seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, severe depression), (**b**) "**persistent or significant disability / incapacity**" and (**c**) "**other serious medical condition**".
f. Congenital abnormality/ birth defect.

**2.8.3 Abnormally low anthropometric values**

Abnormally low anthropometric outcomes were:

a. Percentage of children who are wasted, i.e. with weight-for-length z-score less than -2 **(i.e WLZ < -2**) at 3, 6, 12 and 18 months of age.
b. Percentage of children severely wasted, i.e. with weight-for-length z-score less than -3 (**WLZ < -3)** at 3, 6, 12 and 18 months of age.

**2.9 Analysis principles**

- The primary analysis will be by intention-to-treat. That is, results for all women enrolled (including data on their infants) will be analyzed according to the group to which they were assigned regardless of any protocol violations. Data on subjects who were lost to follow-up because of death, travel from the study site, or refusal to continue with the study will be included in the analysis if available.
- All tests will be two-sided, at 5% level of significance.
- Where more than 10% of observations are missing for a dependent variable, we will report the number of observations used in the analysis.

## 3.0 Design

### 3.1 Sample size and power

Sample size calculations were based on being able to detect an effect size of 0.3 (difference between groups, divided by the pooled SD) for each outcome, assuming 3 groups, power of 80% and alpha=0.05. This required 216 per group, for a total of 648 subjects. Allowing for up to 25% loss to follow-up by 18 months, we needed to recruit 864 subjects. For the biochemical outcomes, we assumed an effect size of at least 0.5, which required a subsample of 79 per group, for a total of 315 subjects after allowing for attrition.

### 3.2 Informed consent issues

All eligible women did sign or thumbprint informed consent for their own participation and for the participation of their babies (upon delivery) prior to being enrolled. If a participant or their parent (in the case of infants) withdraws consent (refuse to continue in the study) at any point of the study, then we will stop any study treatment or follow-up, and if the participant is a pregnant woman, we will advise her to obtain routine supplements from the antenatal clinic. Data on participants who refuse to continue in the study will be included in our analysis on the intention-to-treat basis. However, the primary outcome data for such participants, if missing, will not be imputed.

### 3.3 Treatment groups

Study participants who completed baseline anthropometric and laboratory assessments were randomized into three groups using block randomization, to ensure even distribution of groups across time. Sealed, opaque envelopes bearing the group designations were prepared (by Study Statistician) and arranged in groups (Blocks), each block containing nine envelopes. There were 96 blocks in all, numbered block #1 to block #96, hence a total of 864 (96 x 9) envelopes. For each woman being randomized, the Study Nurse doing the randomization took the topmost 9 envelopes (i.e. starting with block #1), shuffled the nine envelopes in the block, and then offered the woman a choice of any of the nine. After woman made a pick, Nurse returned the remaining eight envelopes to the top of the pile. This process of presenting nine envelopes at a time for each woman to make a pick continued until there were less than nine envelopes left in the whole pile (block #96).

### 3.4 Data collection and follow-up

The variables on which we collected data, and the forms containing the variables are shown in Appendix A (for women) and Appendix B (for infants).

### 3.5 Interim data analysis

For each of the study outcome measures, we will not perform any interim analysis during the period primary data collection is ongoing. That is, for each outcome variable, analysis will be done only at the end of the data collection for that outcome. However the Data and Safety Monitoring Board (DSMB) and Institutional Review Board (IRB) can request interim analysis of

morbidity and all-cause mortality, by treatment group. In case of any evidence of a difference between treatment groups in morbidity and/ or all-cause mortality, DSMB will inform the Study Management Team and advise the appropriate course of action.

**3.6 Definition**

| Term | Unit of measurement | Severe | Moderate | Mild | General |
|---|---|---|---|---|---|
| Anemia (Women) | Hemoglobin concentration (g/L) | < 70.0 | >= 70.0 to < 100.0 | >=100.0 to < 120.0 | < 120.0 |
| Anemia (infants) | Hemoglobin concentration (g/L) | < 70.0 | >= 70.0 to < 90.0 | >= 90.0 to < 100.0 | < 100.0 |
| Under-weight | Weight-for-age z-score (WHO 2006) | < -3 | >= -3 to < -2 | >= -2 to < -1 | < -2 |
| Stunting | Length-for-age z-score (WHO 2006) | < -3 | >= -3 to < -2 | >= -2 to < -1 | < -2 |
| Wasting | Weight-for-length z-score (WHO 2006) | < -3 | >= -3 to < -2 | >= -2 to < -1 | < -2 |
| Low MUAC for age | MUAC-for-age z-score (WHO 2006) | < -3 | >= -3 to < -2 | >= -2 to < -1 | < -2 |
| Low head circumfer ence-for-age | Head circumference-for-age z-score (WHO 2006) | < -3 | >= -3 to < -2 | >= -2 to < -1 | < -2 |

## 4.0 Statistical analysis

### 4.1 Study flowchart

A participant flow diagram will be prepared in accordance with the CONSORT 2010 guidelines (**Figure 1**).

### 4.2 Procedures for data cleaning

We performed data cleaning at various points during data collection:

a. At the field site, data monitors manually checked all forms for completeness and consistency, and resolved queries before forms were sent to Accra for double entry by two different data entry clerks.
b. At the Accra office, the data manager verified and/or compared the entries by the two entry clerks. Differences between the entries were resolved by re-checking the original (scanned) forms before a common dataset was generated.
c. In Accra, queries generated from the common dataset using special SAS and Stata syntax written by project managers were forwarded to the field office and resolved by rechecking

the original data form (including obtaining clarification from the field worker who completed the form), or by a repeat home visit whenever possible.

**4.3 Outliers**

- We will check outliers by visually inspecting Box plots and/or histograms of individual continuous variables, and scatterplots of related variables.
- Outliers which are clearly impossible or implausible values will be corrected if possible, or recoded to missing if correction is not possible.
- Outliers which are plausible or possible will be kept. In analysis of secondary outcomes, variables with outliers will be transformed, and in an extreme situation, a sensitivity analysis will be done to determine if such outliers have undue influence on the results.

**4.4 Software**

All analyses will be done using SAS version 9.3 (SAS Inst. Cary, NC, USA) or Stata version 10.1 or higher (StataCorp, TX, USA). The WHO 2006 Child Growth Standards will be used for age-and-sex standardization of child weight, length, head circumference, arm circumference and weight-for-height.

**4.5 Background characteristics of participants and baseline comparisons**

For all variables measured (with the exception of some particular socio-economic status variables), the available values at the time of screening, recruitment or enrolment, prior to the first intake of the study supplement will be considered as background or baseline characteristics. The background characteristics of subjects who completed the study will be presented in a table, by treatment group. **Table 1a** will be used in analysis involving women, and **Table 1b** in analysis involving infants. However, for specific papers, only selected background characteristics considered relevant to those papers will be presented.

Analysis of background characteristics will be completed as follows:

- We will use frequencies and percentages to summarize categorical data. Percentages will be calculated based on the number of participants for whom data are available.
- Continuous variables will be summarized using either mean and SD for variables, or median and range.
- Where data for certain participants are missing, the number of participants included in the analysis will be indicated.

**4.6 Potential effect modifiers**

The following variables will be considered as effect modifiers:

a. Baseline value for the outcome being analyzed (with the exception of birth outcomes, where baseline values are not possible)
b. Proxy variable for household food insecurity
c. Proxy variable for household socio-economic status or wealth
d. Parity or order of pregnancy
e. Maternal height

f. Maternal BMI at enrolment (adjusted for gestational age)
g. Maternal anemia at enrolment
h. Gestational age at enrolment
i. Season at enrollment
j. Maternal age
k. Maternal education
l. Sex of child (in analyses involving children)
m. One or several proxy indicators for diet quality

The specific effect modifiers that will be considered in each analysis have been indicated in the sections below.

**4.7 Timing of measurement of outcome variables**

The outcome variables were measured after enrolled women had started taking the study supplements. The table below shows the timing of measurement of the outcome variables.

**i.** Women

| **Variable** | **Measurement** |
|---|---|
| Morbidity and supplement intake | Measured every two weeks (± 7 days) after enrolment (beginning of supplement intake) until 6 months (± 1 month) post-partum. |
| Food Frequency and anthropometric and blood indices | Measured at 36 gestational weeks and 6 months post-partum. In practice, measurement at 36 gestational weeks occurred when woman was at least 36 gestational weeks and had not yet delivered. Measurement was considered missed after woman had delivered.<br><br>Measurement at 6 months post-partum occurred within one month of turning 6 months post-partum. |
| Urinary indices | Measured at 36 gestational weeks. In practice, measurement occurred when woman was at least 36 gestational weeks and had not yet delivered. Measurement was considered missed after woman had delivered. |
| Saliva indices | Measured at 28 and 36 gestational weeks. In practice, measurement at the 28 gestational weeks occurred within two weeks of reaching 28 weeks. The measurement at 36 gestational weeks occurred when woman was at least 36 gestational weeks, and had not yet delivered, and was considered missed after woman had delivered. |

**ii.** Infants

| **Variable** | **Measurement** |
|---|---|
| Morbidity and supplement intake | Measured weekly (±3 days) during home visits from birth to completed 18 months of age. |
| Food frequency at 0-5 months | Measured within one week of child's monthly anniversary |

| Variable | Measurement |
|---|---|
| of age | from 0 to 5 months of age. |
| Food frequency at 6, 9, 12, 15 and 18 months of age | Measured within one week of turning 6, 9, 12, 15 and 18 months of age. |
| Anthropometric indices | Measured within 48 hours after birth, and at 3, 6, 12 and 18 completed months of age. |
| Blood indices | Measured within three weeks of turning 6 months of age, and also at 18 completed months of age. |

**4.8 Analysis of the effect of the intervention**

The analysis of the effect of the intervention (at single time points or repeated measures) will begin with testing the null hypothesis of no difference among the three treatment groups using ANCOVA or logistic regression, and controlling for pre-specified covariates including, in the case of women, baseline values. Because infants will not have true baseline values unaffected by intervention, most of the covariates used in analyses involving infants will be mothers' baseline characteristics. Only covariates significantly associated with an outcome at 10% level of significance in a bivariate analysis will be include in the final adjusted analysis. This means we may have different sets of covariates for each outcome.

For all analyses, if the global null hypothesis is rejected at 0.05 level, then we will perform post-hoc pairwise comparisons of all three groups using Tukey-Kramer adjustment (for continuous variables) or the "Contrast" statements (for categorical variables) in SAS. We will also use Scheffe's test to assess whether the LNS group differs from the non-LNS groups with respect to most outcomes, and whether the IFA group differs from the non-IFA groups with respect to iron outcomes or variables such as morbidity which might be affected by iron status.

The effects of potential effect modifiers will be assessed with an interaction term in the ANCOVA or logistic regression model. Significant interactions ($p < 0.05$) will be further examined with stratified analyses, estimation of separate regression lines, or estimation of adjusted means at key points of the covariate, in order to understand the nature of the effect modification.

**4.9 Comparison of primary outcomes at birth and 18 months of age**

The ANCOVA to determine the effects of the intervention on birth length (crude length and length-for-age z-score) and length-for-age z-score at 18 mo among the three intervention groups will be performed using PROC GLM. Results will be summarized as mean and SD and tabulated, by group (**Table 2** and **Table 3**).

**4.10 Comparison of secondary outcomes**

**i. Comparison at single time points**

Comparison of secondary outcomes at single time points will be performed using PROC GLM (for continuous outcome variables), and PROC FREQ and PROC LOGISTIC for categorical outcome variables. Continuous variables will be summarized using either mean and SD, or median and range. Categorical variables will be summarized using percentages and Odds Ratios, with 95% Confidence Intervals (95% CI).

Analysis of several secondary outcomes at birth and 18 months of age will be presented alongside the primary outcomes in **Table 2** and **Table 3** as well as in **Table 4**. Prior to the analysis of additional secondary outcomes at other single time points, this SAP will be updated to include those specific single time points, and how results will be presented.

**ii. Comparison of repeated measures**

For continuous outcome variables, a linear mixed model (PROC MIXED) will be used to compare patterns in the outcome variables across time among the groups. For categorical variables, a variant mixed model logistic regression (SAS PROC GLIMMIX) will be used. Prior to analysis of repeated measures, this SAP will be updated to include the specific analyses and the presentation of the results.

### 4.11 Selection of covariates and effect modifiers in the analysis of primary outcomes

Below we list the two primary outcomes to be analyzed (both at single time points), and indicate the covariates and effect modifiers that will be used for each analysis. Each of the effect modifiers will be considered separately in the regression model to avoid collinearity.

| **Primary outcome variable** | **Analysis** | **Covariates** | **Effect modifiers** |
|---|---|---|---|
| Birth length (crude length in cm and length-for-age z-score) | ANCOVA (SAS Proc glm) | - Maternal height<br>- Maternal BMI<br>- Gestational age at enrolment<br>- Maternal age<br>- Child sex<br>- Maternal education<br>- Proxy for SES<br>- Parity<br>- Season at enrolment<br>- Mother's marital status | - Maternal height<br>- Maternal BMI<br>- Gestational age at enrollment<br>- Maternal age<br>- Child sex<br>- Maternal education<br>- Proxy for SES<br>- Parity<br>- Season at enrolment<br>- Maternal anemia at enrollment |
| Length-for-age z-score at 18 months | ANCOVA (SAS Proc glm) | - Maternal height<br>- Maternal BMI<br>- Gestational age at enrolment<br>- Maternal age<br>- Child sex<br>- Maternal education<br>- Proxy for SES<br>- Parity<br>- Season at enrolment | - Maternal height<br>- Maternal BMI<br>- Gestational age at enrollment<br>- Maternal age<br>- Child sex<br>- Maternal education<br>- Proxy for SES<br>- Parity<br>- Season at enrolment |

| Primary outcome variable | Analysis | Covariates | Effect modifiers |
|---|---|---|---|
| | | - Mother's marital status | - Maternal anemia at enrollment |

**4.12 Selection of covariates and effect modifiers in the analysis of secondary outcomes**
Prior to analyses for secondary outcomes, this SAP will be updated with an *a priori* list of covariates and effect modifiers, as has been done for the primary outcomes above.

**4.13 Data transformation**
Based on previous studies, we expect the primary outcome variables (birth length – crude length in cm and length-for-age z-score – measured within 48 hours of delivery and length-for-age z-score at 18 months of age) to be normally distributed. Continuous outcomes will be assessed for conformance to the normal distribution and will be transformed appropriately. If no suitable transformation can be found to optimize normality and homogeneity of variances, analysis will be done on ranked data. Also see section 4.3 (Outliers).

**4.14 Confidence intervals**
Estimates of treatment effects will be accompanied by a 95 % confidence interval, wherever possible.

## Tables

**Table 1a**
Baseline characteristics of women who completed the study

| **Variable** | **IFA ($\bar{x}$ ± SD) [n]** | **MMN ($\bar{x}$ ± SD) [n]** | **LNS ($\bar{x}$ ± SD) [n]** | **P-value** | **Test** |
|---|---|---|---|---|---|
| Number of participants | x.x | x.x | x.x | | |
| Age, y | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Years of formal education | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Marital status (% [n]) | x.x [x] | x.x [x] | x.x [x] | x.xx | Chisq |
| Proxy for socioeconomic status | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Parity | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Weight (kg) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Height (m) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| BMI ($kg/m^2$) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mid upper arm circumf. (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Triceps skinfold (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Gestational age at enrolment | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Hemoglobin | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Positive rapid test for malaria (%) | x.x [x] | x.x [x] | x.x [x] | x.xx | Chisq |
| Elevated Acute phase response (%) | x.x [x] | x.x [x] | x.x [x] | x.xx | Chisq |
| ZPP | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| TfR | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Ferritin (geometric mean) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Anemia (%) | xxx/ xxx (xx) | xxx/ xxx (xx) | xxx/ xxx (xx) | x.xx | Chisq |
| Plasma lipid profile | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | Chisq |

**Table 1b**
Baseline characteristics of infants who completed the study

| **Variable** | **IFA ($\bar{x}$ ± SD) [n]** | **MMN ($\bar{x}$ ± SD) [n]** | **LNS ($\bar{x}$ ± SD) [n]** | **P-value** | **Test** |
|---|---|---|---|---|---|
| Number of participants | x.x | x.x | x.x | | |
| Mother's education (y) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mother's marital status (% [n]) | x.x [x] | x.x [x] | x.x [x] | x.xx | Chisq |
| Number of persons in the household | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | | Kruskal Wallis |
| Children <5 y in the household | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | | Kruskal Wallis |
| Proxy household socioeconomic status | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Parity | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mother's weight (kg) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mother's height (m) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mother's BMI ($kg/m^2$) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mother's mid upper arm circumf. (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mother's triceps skinfold (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |
| Mother's gestational age at enrolment | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANOVA |

**Table 2**
Indices of pregnancy outcome, by group

| **Variable** | **IFA ($\bar{x}$ ± SD) [n]** | **MMN ($\bar{x}$ ± SD) [n]** | **LNS ($\bar{x}$ ± SD) [n]** | **P-value** | **Test** |
|---|---|---|---|---|---|
| Gestational age delivery (wk) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | | ANCOVA |
| Birth weight (kg) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Birth length (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Head Circumference at birth (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| MUAC at birth (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Weight-for-age z-score | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Length-for-age z-score | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Weight-for-length z-score | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Head circumf.-for-age z-score | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Low birth weight (% (95% CI)) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |
| Premature delivery (% (95% CI)) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |

**Table 3**
Comparison of anthropometric status in the intervention groups at 18 months

| **Variable** | **IFA ($\bar{x}$ ± SD) [n]** | **MMN ($\bar{x}$ ± SD) [n]** | **LNS ($\bar{x}$ ± SD) [n]** | **P-value** | **Test** |
|---|---|---|---|---|---|
| Weight (kg) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Length (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| MUAC (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Head circumference (cm) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Weight-for-age z-score (SD) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Length-for-age z-score (SD) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Weight-for-length z-score (SD) | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Head circumference-for-age z-score | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |
| Arm circumference-for-age z-score | x.x ± x.x [x] | x.x ± x.x [x] | x.x ± x.x [x] | x.xx | ANCOVA |

**Table 4**
Prevalence of malnutrition at 18 months of age and adjusted odds ratio (AOR) and 95% CI estimates of the effect of LNS supplementation on malnutrition

| **Variable** | **IFA (n)** | **MMN (n)** | **LNS (n)** | **P-value (n)** | **Test** |
|---|---|---|---|---|---|
| Percentage underweight (WAZ < -2) [% (95% CI)] | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |
| AOR (95% CI) | x.x (x.x - x.x) | x.x (x.x - x.x) | -- | | Logistic regression |
| Percentage stunted (LAZ < -2) [% (95% CI)] | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |
| | x.x (x.x - x.x) | x.x (x.x - x.x) | -- | | Logistic regression |
| Percentage wasted (WLZ < -2) [% (95% CI)] | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |
| AOR (95% CI) | x.x (x.x - x.x) | x.x (x.x - x.x) | -- | | Logistic regression |
| Percentage severely underweight (WAZ < -3) [% (95% CI)] | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |
| AOR (95% CI) | x.x (x.x - x.x) | x.x (x.x - x.x) | -- | | Logistic regression |
| Percentage severely stunted (LAZ < -3) [% (95% CI)] | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |
| AOR (95% CI) | x.x (x.x - x.x) | x.x (x.x - x.x) | -- | | Logistic regression |
| Percentage severely wasted (WLZ < -3) [% (95% CI)] | x.x (x.x - x.x) | x.x (x.x - x.x) | x.x (x.x - x.x) | x.xx | FREQ |
| AOR (95% CI) | x.x (x.x - x.x) | x.x (x.x - x.x) | -- | | Logistic regression |

**List of figures**