Prevention of Linear Growth Faltering in Infants and Young Children With Lipid-based Nutrient Supplements (iLiNS-DOSE)

Statistical Analysis Plan

Version 05.0 (25.04.2015), includes 6 appendixes

Prepared by:

Lotta Alho, MSc, study statistician

Yin Bun Cheung, PhD, responsible study statistician

Jan Peerson, MSc, study statistician

Approved by:

Name, degree	**Position**	**Signature**
Kenneth Maleta, MBBS, PhD	Principal investigator	
Per Ashorn, MD, PhD	Co-Principal investigator	
Ulla Ashorn, PhD	Responsible investigator, social studies	
Kathryn Dewey, PhD	Principal investigator for the iLiNS-Project	
Steve Vosti, PhD	Responsible investigator, economic studies	

Contact details: Ms. Lotta Alho, University of Tampere School of Medicine, Finland. Email: Lotta.Alho@uta.fi

Table of Contents

1 Version history

Version number	Version date	Prepared by	Description of the completed editions
01.0	17.03.2013	Lotta Alho Yin Bun Cheung Jan Peerson	Original document (includes appendix 01)
0.20	07.05.2013	Alho, Cheung, Peerson Beth Prado, Chiza Kumwenda	Added Appendix 02: Developmental outcomes at age 18 months (prepared by Beth Prado) and Appendix 03: Breast milk intakes (prepared by Chiza Kumwenda)
03.0	24.05.2013	Alho, Cheung, Peerson Anna Pulakka	Added Appendix 04: The effect of LNS on physical activity (prepared by Anna Pulakka)
04.0	26.07.2013	Alho, Cheung, Peerson Mary Arimond	Added Appendix 05: Effect on infant and young child feeding practices (prepared by Mary Arimond)
0.50	25.04.2014	Alho, Cheung, Peerson Aleks Schaefer	Main growth SAP: Edited the way SAE's are claculated and presented. Removed adjustment for time in the study and presenting total number of cases per group. Added Appendix 6: Hypothetical Willingness-to-Pay for LNS and Likuni Phala at Baseline (Prepared by Aleks Schaefer)

2 Introduction

Poor growth and severe childhood stunting are very common in rural Malawi and elsewhere in Sub-Sahara Africa, with known negative consequences for child development and long-term individual and household welfare. To date, few interventions have proven successful in promoting linear growth in early childhood. Preliminary results from Malawi and Ghana suggest that a 6-12 month-long daily complementary feeding of infants with 20-50 g of an energy-dense and highly micronutrient fortified Lipid-based Nutrient Supplement (LNS) may markedly reduce the incidence of severe stunting before the age of 18 months.

The iLiNS-DOSE trial was designed to study the impact of a 12-month LNS provision to infants and young children on their growth, nutritional status and a number of other health outcomes. For this purpose, a total of 1932 infants were enrolled in rural Malawi, randomized to receive for 12 months either no supplement or one of five alternative LNS-preparations (six study groups in total), and intensely monitored for 12-months for a large number of outcomes. Key details of the trial have been recorded at the clinical trial registry at the National Institutes of Health (USA) (www.clinicaltrials.gov), under the registration number NCT00945698. A full trial protocol is available from the contact person to this document.

This document (called "the statistical analysis plan" or SAP) describes the study group's plan for data analysis, management, and storage. The SAP is designed to be evolving over time. Version 1.0 documents the details of the hypothesis testing and other analyses on primary and selected secondary outcomes. Subsequent versions of the SAP will give further details on the analyses and hypothesis testing of additional secondary outcome variables and exploratory analyses from the data.

3 Study objectives

The main aim of the trial is to assess the safety and impact of LNS supplementation on linear growth of infants and young children and to identify individual, household, and village-level characteristics that would modify the effects of LNS on child growth. A secondary aim is to similarly study the impact of LNS on various other (secondary) outcomes in the same target group. Finally, the trial aims to provide descriptive information on issues that might be necessary to facilitate future demand creation for LNS interventions.

The above aims have been broken down into the following first five objectives that were predefined in the trial protocol. The safety aim was not explicitly stated among the predefined objectives in the trial protocol, but was listed under the primary outcomes for analysis.

1. To determine the lowest daily dose of LNS that will promote linear growth among 6-18 months old infants in a rural Malawian community with poor food security. *This covers also the objective to study if ANY dose of LNS promotes linear growth among the target group.*

2. To assess if LNS made without milk has a linear growth-promoting effect comparable to that of milk-containing LNS (in the above described environment, with 20 and 40 g/day ration sizes).

3. To determine the impact of five different LNS supplementation schemes on child dietary intake, morbidity, appetite, micronutrient status, immune function, and neuro-behavioral development.

4. To collect information to facilitate future demand creation for LNS interventions, such as end-user knowledge, attitudes and practices related to LNS and other feeding and parental care-giving practices.

5. To assess the extent to which household food insecurity and other individual, household, and village-level characteristics modify the effects of LNS on child outcomes.

6. To determine if any of the LNS supplements lead to increased risk of serious adverse events.

4 General approach to data analysis

There will be three categories of data analysis.

1. For the main aim (safety and linear growth outcomes), the analyses will be driven by predefined primary study hypotheses (see chapter 4 below). Conclusions on this part of the study will be based on formal hypothesis testing.

2. For the secondary aim (other outcomes), the analyses will be driven by similar hypotheses to those used for linear growth. These hypotheses have not been predefined in the trial protocol and hence they do not appear in version 1.0 of this SAP. They will, however, be defined as appendixes in subsequent versions of the SAP. For each hypothesis-driven analysis, the SAP will be updated prior to starting the analysis.

3. In addition to the hypothesis-driven questions, there will be a large number of exploratory analyses. In the absence of predefined study hypotheses, these analyses will be considered hypothesis-generating, rather than confirmatory.

5 Hypotheses to be tested

As indicated above, version 1.0 of the SAP describes predefined hypotheses only for the linear growth outcomes, i.e. specific objectives 1 and 2. Further hypotheses will be formulated and documented in subsequent SAP versions before the respective analyses are started.

Objective 1 / hypothesis 1: The change in mean length-for-age Z-score (LAZ) of infants provided with 10, 20, or 40 g/day of LNS from 6 to 18 months of age will be greater than that of infants who receive no dietary intervention at the same age.

Objective 2 / hypothesis 2: The change in mean LAZ of infants receiving 20 or 40 g/day of LNS without milk from 6 to 18 months of age will not be lower than that of infants receiving a comparable intervention with milk-containing LNS.

6 Data cleaning and procedures on breaking the intervention code

The study group will adopt the following procedures for data cleaning and breaking the intervention code

1. In the first phase, a number of investigators will do preliminary cleaning of the data required to the main analyses (safety and linear growth outcomes). At this point, all investigators are totally blinded to the intervention each participant has been receiving.

2. A study statistician (L.A) makes a preliminary database that contains semi-clean data required for the main analyses. The database and summary statistics for each variable are distributed to the principal investigators, the members of the board governing trial implementation and the principal biostatistician for the trial. Once these individuals agree that the data are sufficiently comprehensive and clean, the study statisticians (L.A, J.P, and Y.B.C) are provided with the database and a code that can be used to group the participants who received the same intervention together – i.e. that gives group codes 1, 2, 3, 4, 5, and 6 without indicating the actual intervention each group number relates to.

3. The study statisticians review the data and complete preliminary analyses for group comparisons (without knowing the actual interventions). Based on these analyses, the study statisticians make suggestions for the amendment of the SAP (e.g. on the treatment of missing values). The investigators listed under 2) above then agree on a revised version of the SAP, after which the intervention code is broken and the main analyses are completed.

4. For secondary outcomes, the analyses will be mostly completed by investigators who are not study statisticians. For each of these analyses, data cleaning will be completed as above. Once the analyst has completed the first round of data cleaning without any knowledge about the group information, s/he will request scrambled group information from the

statisticians. This information will again group the participants who received the same intervention together without indicating the actual intervention each group number relates to. For each analyst, the study statisticians provide a new / different set of scrambled group codes – so that two analysts cannot combine their results during the analysis.

4. Before the intervention code is fully broken, mistakes found in the data can be corrected in the database, as long as there is an audit trail that indicates the date of correction, the old and new value, justification for the correction and the identity of the person authorizing the change (this is not necessary for the correction of entry errors). After the code is broken, the data on main outcomes will be "frozen" and data can no longer be corrected in the database. Instead, all corrections (also entry errors) will be reviewed and need to be approved by the responsible investigator and documented before programmed into cumulative syntax-files (do-files, one for each data collection form) that will contain the same information as the audit trail described above. These do-files need to be run to clean the data before any subsequent analyses.

5. Data cleaning for other data not used for the main analyses will continue even after breaking the intervention code. For each additional data collection form, the data will be similarly frozen by the time first real analyses will be completed from them (the time can vary form by form). Also for these forms, mistakes found before data freezing will be corrected straight into the database whereas those found after the data freezing will be corrected in separate data-cleaning do files. Both correction methods will contain the audit trail that can be used to track all completed changes.

6. Any investigator may raise a suspicion for a correctable mistake in the data. If such a suspicion arises, the investigator who has the responsibility over those particular data (each data collection form has a defined responsible investigator) should be informed and s/he should investigate if a correction is needed. If yes, the data managers in Finland and Malawi will be informed and the change will be made and documented either to the database (before data freezing, this will be done in Malawi), or to a correction do-file (after data freezing, this will be done in Finland).

7 Definition of the primary outcomes

Change in length-for-age Z-score (LAZ):

Length for age will be determined from age, sex, and length information at six months (visit 0) and 18 months (visit 52) of participant age, using the Stata macro developed by the WHO using the WHO 2006 multi-centre growth standard. The values will be rounded to two decimal points. The change (expressed with two decimals) will be calculated by subtracting the value at 6

months from the value at 18 months of age. *The data will be extracted from Form 00: Q2.5; Form 04: Q1.2, Q2.2*

8 Safety outcomes

Incidence of serious adverse events (SAE) during the observation period.

SAE will be defined as an event determined to be an SAE by the study physician. The SAEs will be categorized into five categories: Death, life threatening event, inpatient hospitalization, significant disability or other serious adverse event. *The data will be extracted from Form 29, Q3.2.*

9 Basis for the analysis: Intention to treat and per protocol

Primarily, the analysis will be based on the principle of modified intention-to-treat. The modification concerns six participants who were accidentally allocated to another group than actually randomized. For each participant, the randomization code was pre-packed and sealed in an individual envelope that was opened and used for group allocation at enrolment. For these 6 individuals, the randomizer made a recording error, i.e. s/he noted down in a data collection form an incorrect group code or wrote the code with unclear handwriting. The incorrect code was later transcribed into the computer software that was used to plan participant visits and allocate interventions. These six participants were told to belong to the erroneously recorded intervention group and they received that intervention throughout the trial – hence they will also be analyzed in that group (rather than the one written on the randomization slip).

All randomized participants are eligible to be included in the analyses, with the exception that subjects with missing data on an outcome variable will be excluded for the analysis of that outcome. For variables targeted to be measured every 6-months, the data are considered missing if the actual measurement date is over +/- 8 weeks from target.

Number of participants with non-missing values analyzed for each end point will be presented by treatment groups.

Besides the intention to treat, there will be two per protocol analyses, adjusting for the adherence to the dietary supplementation. In the first per protocol analysis, the statistical model will include a variable that indicates the number of intervention doses delivered to the participant during the time period for which the participant received the study supplements (the supplements were delivered every two weeks). In the second per protocol analysis, the statistical model will include a related variable that indicates the number of days when the participant's guardian indicated that the participant had eaten the study supplement (this information was collected on a daily basis).

10 Time points for the analyses

All the main analyses will primarily cover the period from enrolment (when the participants are 6 months old) to the end of the intervention (when the participants are 18 months old).

Secondarily, there will be a growth analysis after a 2-year post-intervention period, i.e. covering a period from enrolment to when the participants are 42 months old. SAE data will not be collected or analyzed after the participants have turned 18 months old.

11 Presentation of the study findings and hypothesis testing

11.1 Success of enrolment and follow-up

All registered participants and the success of their follow-up will be described in a flow chart (Figure 1). For additional information drop-out rate between groups will be tested with Fisher's exact test and baseline characteristics of drop-outs compared to those who completed the study will be tested with t-test or chi square. P-values for these tests will be shown in the text.

11.2 Baseline information

Participant characteristics at enrollment will be tabulated by treatment arms as indicated in tables 1a and 1b. Hypothesis testing will be performed for baseline information to give additional information but p-values will not be presented in Table 1 of the eventual manuscript. Methods used for hypothesis testing are indicated in Tables 1a and 1b.

11.3 Comparison of the change in length-for-age Z-score between intervention groups versus the control group

Box-whisker plots of the change in LAZ of all 6 groups will be shown side by side in Figure 2. The group means and standard deviations for the change in length (in cm) and LAZ (in z-score units) will be presented as indicated in Table 2. The table will also tabulate the difference in mean length and LAZ and their 95% confidence intervals between the control group and each of the intervention groups.

Mean change in LAZ in each of the intervention groups will be individually compared against that of the control group using a two-sample t-test. The Holm's method will be used to adjust for the multiple comparisons (Aickin & Gensler, 1996). The raw P-values are presented in tables but the text and conclusion will be based on the Holm-adjusted P-values.

The null-hypothesis of LNS having no impact on linear growth is rejected for each comparison that yields a Holm's adjusted p-value <0.05.

11.4 Comparison of milk-containing and milk-free LNS

This analysis will exclude participants who received no intervention or 10 g / day milk-containing LNS. An ordinary least-square regression of the following form will be estimated:

$$\hat{y}_i = b_0 + b_1 D_i + b_2 S_i + b_3 (D_i \times S_i)$$

where D= 0 or 1 for the 20g and 40g group, respectively, and S= 0 or 1 for the milk and milk-free LNS group, respectively. If the coefficient b3 for the interaction term does not reach a significance level of P<0.10, a simpler model without the interaction term will be estimated. 90% CI will be provided for each parameter. Ninety per cent instead of 95% CI is used because the non-inferiority consideration is one-sided and the use of 90% CI is the convention in this setting (Senn, 1997). Both models will be shown in table 3. Conclusion is to be based on the simpler model if the interaction term is not statistically significant (P>0.10), or vice versa.

Evaluation

The set non-inferiority margin for this analysis will be 0.15 Z-score units. If the lower bound of the 90% CI of the coefficient b2 is larger than -0.15, non-inferiority is confirmed. If the upper bound of the 90% CI is smaller than -0.15, inferiority is confirmed. If the upper and lower bounds of the 90% CI are larger and smaller, respectively, than -0.15, the finding is not conclusive.

If there is no significant interaction, the above evaluation only need be done once using the simple regression model without interaction. If there is significant interaction (P<0.10), the above evaluation will be done twice based on the model with interaction: Firstly on the 90% CI of the b2 coefficient concerning the non-inferiority of milk-free LNS in the 20g dose. Secondly on the 90% CI of the (b2+b3), obtained by the linearly combination command (Stata's **lincom**), concerning the non-inferiority of milk-free LNS in the 40g group.

11.5 Safety profile: Analysis of serious adverse events

The total number of serious adverse events (SAEs) will be presented by intervention group and SAE categorization, as indicated in Table 4. There will also be an analysis on the proportion of participants with at least one episode of SAE. For each of the intervention groups, the proportion and a relative risk (as compared to the control) will be presented as indicated in table 4. Fisher's exact test will be used to test the global null hypothesis of no differences between groups and the null hypothesis will be rejected if P<0.05. If the global null hypothesis is rejected, comparison between each intervention group and the control group will be conducted using log-binomial regression. Rate ratios (95% CI) for the incidence of any SAE will be calculated for each intervention group (as compared to the control group).

AE information was not collected after the participants had finished the intervention and completed the primary outcome study visit at 18 months of age.

Cumulative incidence curve for mortality will be presented graphically by intervention group as illustrated in Figure 3. The log-rank test will be used for testing global hypothesis and pair-wise comparisons. Hypothesis of equality of survivor functions is rejected if $P<0.05$. Hazard ratios and their confidence intervals will be estimated by the Cox regression model. The **sts** and **stcox** commands will be used.

12 General notes on statistical methods

12.1 Software

All analyses will be done in Stata version 12. The WHO 2006 multi-centre growth standard will be used for age-and-sex standardization of weight, length (height), weight-for-height, MUAC and head circumference.

12.2 Preparing anthropometric data for analysis

All the anthropometric measurements were completed in triplicate during each study visit. But for the analysis, the team will use the mean of the first two readings if they do not differ more than by a pre-specified tolerance limit. If they do, the third measurement will be compared with the first and second measurements and the pair of measurements that has smaller difference will be used to calculate the mean which will be used in analyses. If there are only one or two repeated measurements mean of those two will be used for the analyses.

The agreed tolerance limits between the first two measurements are:

1. length/height ≤ 0.5 cm
2. circumferences (head, MUAC) ≤ 0.5 cm
3. infant/child weight ≤ 0.1 kg
4. adult weight ≤ 0.1 kg
5. skinfold thickness ≤ 2.0 mm

The length, circumference and skinfold thickness measurements were recorded to last complete unit (mm). To account for the bias of always rounding the values a bit downwards, half a unit will be added to all length, circumference and skinfold thickness measurements prior to the analysis. This procedure is not done for weight measurements, since they were recorded accurately with electronic scales.

Missing growth values will be treated as missing, i.e. there will be no growth data imputation from the other data. Imputation is considered unreliable due to long time-interval between anthropometric measurements, at an age when growth faltering is common.

When measuring change in anthropometric values between two time intervals, the change will be treated as missing if there is a missing value in either of the respective time points.

12.3 Multiple comparisons

The study involves multiple objectives and therefore multiple sets of hypothesis. Statistically, the different sets of hypotheses are considered independent families of hypotheses. Statistical adjustment for multiple comparisons in one family of hypotheses does not need to consider the other families.

For efficacy analysis, each family consists of 5 hypotheses, each comparing an intervention group versus the control group. The Holm's adjustment method is used.

For safety analysis, it is preferable to err on the cautious side (Nauta, 2010). We began with testing the global null hypothesis of no difference between groups. If the global null hypothesis is rejected, raw P-values are used in the comparisons between intervention and control groups.

12.4 Confidence intervals

Regardless of results in hypothesis testing, the calculated ratios and differences in between-group comparisons will be complemented with confidence intervals (usually at 95% level but 90% for non-inferiority studies), for descriptive purpose. For the quantitative outcomes, confidence intervals will be based on t-test. For binary outcomes, the confidence intervals will be based on binomial distribution.

12.5 Interaction and effect modification

There will be two sets of test for interaction between the intervention group and selected other variables on their association with the primary outcome (change in length-for-age z-score). All tests will be done using the likelihood ratio test.

The first set of analyses will be hypothesis-driven and will include unambiguous predefined variables that could logically modify the effect of the nutritional intervention on infancy and early childhood growth. Variables included (as continuous variables where possible) in this analysis include:

1. The participant's baseline length-for-age (below / above median)
2. Maternal BMI at enrolment
3. Maternal height
4. Maternal age
5. Maternal parity
6. The participant's sex
7. Number of under-five year old children in the household
8. Cohabitation of the child's father with the rest of the family (yes / no)

9. Household food security

The second set of analyses will be exploratory in nature and will include variables that can be constructed in several ways or that cannot a priori be logically linked to an effect modification. Themes or variables included in this analysis include:

1. Maternal knowledge, attitudes, and practices around child nutrition
2. Household wealth

If a statistically significant interaction ($p<0.1$) is found, the outcome analysis will be completed as stratified by the respective predictor variable. Variables that show no interaction with the intervention group can be used as covariates in the main analysis.

12.6 Covariate adjustment

The final decision on the use of covariates in main analyses will be decided based on preliminary analyses on the final dataset that includes information on the clustering of participants in the same group but does not provide information on the actual intervention delivered to each group.

At this stage, four different regression models for change in LAZ will be constructed, first of these with no covariate adjustments and models 2-4 with various adjustments. If the point-estimates for the regression co-efficient for the intervention group differ in any of the models by more than 10% from that in the unadjusted analyses, the adjusted analysis will be primarily presented in the eventual publications. If all the differences are smaller than 10% (Maldonado & Greenland, 1993), the results in the tables will be shown without covariate adjustments, but model 4 results will be provided in the text as supplementary information.

The four models include:

1. No covariate adjustment
2. Adjustment for baseline LAZ-score
3. Adjustment for baseline WHZ-score
4. Adjustment for baseline LAZ-score and baseline WHZ-score and for any of the variables presented in tables 1a and 1b showing statistically significant association (at $p<0.1$ level) with the change in LAZ-score

13 Storage and release of data

The data meta-data will be stored in a tailor-made hierarchical database, consisting of a MS Access front-end and MySQL tables in the back-end. The database, associated metadata, and form –specific do-files that contain all cumulative data corrections for the respective data collection forms are stored at a computer server at the University of Tampere and daily copied to

a server at the Mangochi research site, University of Malawi. A study statistician (L.A) acts as the manager for these data.

When an investigator wishes to perform certain analyses, s/he will request the respective data from the above-indicated data manager. The data manager will export all the data from the respective data collection form into an excel or Stata file, run the cumulative data correction do-file and then provide the corrected data, together with the syntax for the correction do file (that documents all the completed data editions) to the person requesting the data.

The databases and the do-files will be named with systematic naming format and stored at the central server at the University of Tampere. For each article, the following files will be stored:

1. The database from which the analyses were performed
2. The data dictionary
3. The data correction do file(s)
4. The data analysis do file(s)
5. The actual scientific article

The data collection forms and respective user guides will be stored at the central study repository, in the computer server at the University of Tampere

In the longer run, there is a plan to place the data publicly available in the internet.

13.1 Data and output handling

To ensure reproducibility and to keep an audit trail, all data management, analysis and outputting procedures will be kept as Stata **do** files. All transformation, categorisation, or creation of variables as well as keeping or dropping of subjects in specific analyses will be written in the do files. The **do** files are to be executed in order to obtain these new data features temporarily, as opposed to saving these new features into permanent data files. It is envisaged that a large number of commands are required, and they may need to be partitioned in more than one **do** file. Numeric values will be used to indicate the correct sequence for running these files and version number of the do file is indicated at the file name, e.g. iLiNS-DOSE data cleaning01, form 18, v01.0, 2012-12-27.do should be executed before iLiNS-DOSE data analysis02, form 18, v01.0, 2012-12-27. If data from more than one form are used the form number is not indicated in the do-file name but forms are listed in the comments section in the beginning of the do-file. Variables on data version and version date are included in the data file and people using the data are asked not to share the files with other approved data users. All approved users obtain the data from the data manager so that the latest version is distributed. Outputs will be saved as log files.

A master **do** file, for example, may include, but is not limited to, the following commands to execute all the data modification, analyses and outputting procedures in one go:

**** Example of a master do file

```
**** DOSE main paper, master do file

clear

version 11.2

set more off

set mem 50m

cd c:\dose\mainpaper

capture log close

log using mainpaper.log, text replace

do iLiNS-DOSE data cleaning01, form 18, v01.0, 2012-12-27.do

do iLiNS-DOSE data analysis02, form 18, v01.0, 2012-12-27.do

do iLiNS-DOSE data analysis03, form 18, v01.0, 2012-12-27.do

log close
```

14 Procedures and history on modifications to the analysis plan

All new versions of and additions to the statistical plan will be approved by a team of core investigators, consisting of the senior researchers who oversee the trial implementation (iLiNS-Malawi Board of Directors) and the study statisticians. Each version will be identified with a new version number and a date of approval and named with standardized file-name format (iLiNS-DOSE analysis plan, version 00.3, 2012-12-27.docx).

In the file name, the first two digits before the decimal indicate an approved change to the SAP (ie version 01.0 denotes the first approved version, 03.0 the third approved version etc). The last digit after the decimal indicates a yet unapproved revision number for a document under editions (eg. 02.1 points to a document that is based on the second approved version, but has undergone one round of yet unapproved editions to it).

The table below lists the editions made to the different approved versions of the SAP:

Version number	Date of approval	Editions
01.0	xx.xx.2013	Original document

15 References

Aickin M, Gensler H. Adjusting for multiple testing when reporting research Results: The Bonferroni vs Holm Methods. *American Journal of Public Health* 1996; 86(5): 726-728.

Maldonado G, Greenland S. Simulation Study of Confounder-Selection Strategies. *American Journal of Epidemiology* 1993; 138(11): 923-936.

Nauta J. *Statistics in Clinical Vaccine Trials*. Heidelberg. Springer. 2010.

Senn S. *Statistical Issues in Drug Development*. Chichester, GBR. John Wiley & Sons. 1997.

16 Appendixes

Statistical Analysis Plan, Appendix 1: Secondary growth outcomes

Statistical Analysis Plan, Appendix 2: Developmental outcomes at age 18 months (added on 07.05.2013).

Statistical Analysis Plan, Appendix 3: Breast milk intakes (added on 07.05.2013).

Statistical Analysis Plan, Appendix 4: The effect of LNS on physical activity (added on 24.05.2013).

Statistical Analysis Plan, Appendix 5: Effect on infant and young child feeding practices (added on 26.07.2013).

Statistical Analysis Plan, Appendix 6: Hypothetical Willingness-to-Pay for LNS and Likuni Phala at Baseline (added on 25.04.2014).

17 Legends to the figures

Figure 1. Participant flow in CONSORT recommended format (Lancet 2001: 357: 1193)

Figure 2. Box-Whisker plots of change in LAZ by groups

Figure 3. Cumulative incidence curve for mortality, by intervention groups

18 Figures

Figure 1. Participant flow

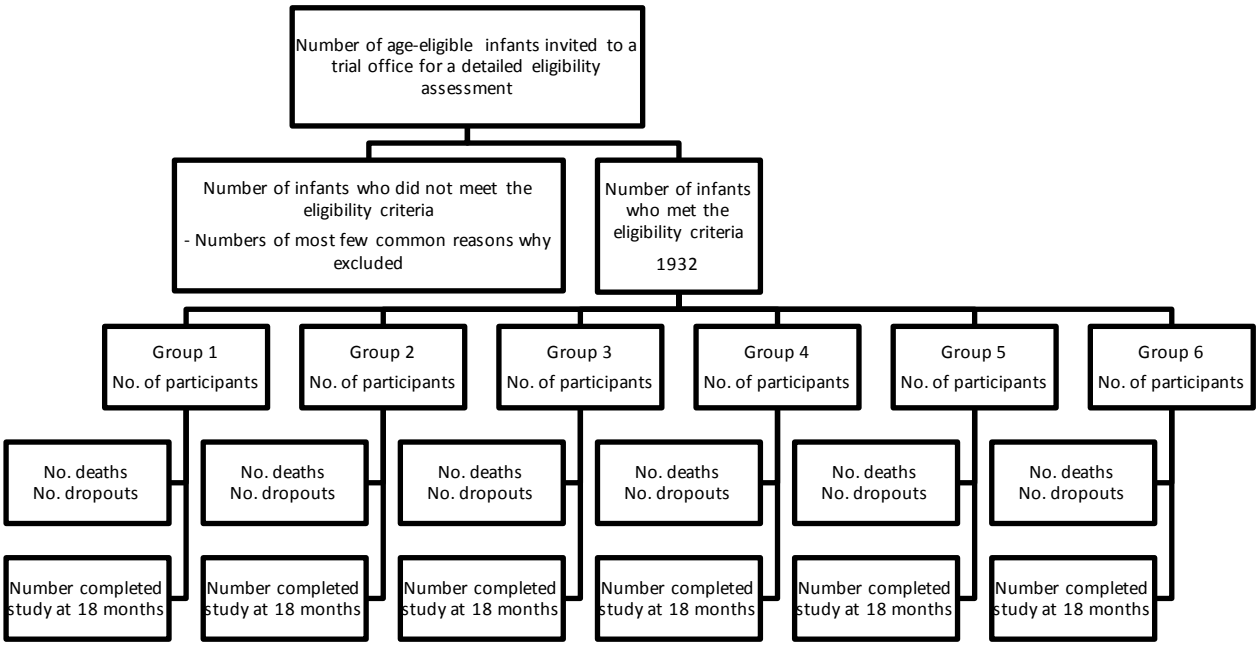

Figure 2. Box-Whisker plots of change in LAZ by groups

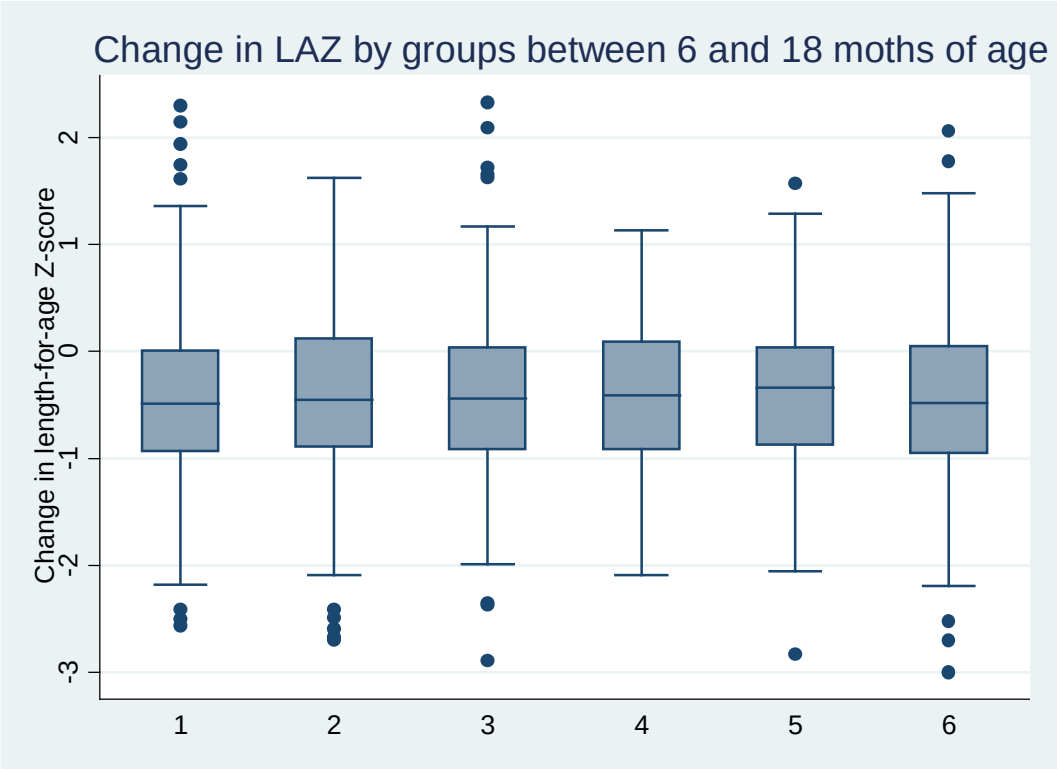

Figure 3. Cumulative incidence curve for mortality, by intervention groups

19 Tables

Table 1a Baseline characteristics of participants at enrolment

Variable	**Control**	**10g milk LNS**	**20g milk LNS**	**20g milk-free LNS**	**40g milk LNS**	**40g milk-free LNS**	**Test**
Number of participants	xxx	xxx	xxx	xxx	xxx	xxx	
Age, months (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Proportion of Males (percentage)	xxx / xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	Chi-squared
Weight, kg (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Length, cm (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Middle upper arm circumference, cm (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Head circumference, cm (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Weight-for-age z-score (mean, SD, N)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	ANOVA
Length-for-age z-score (mean, SD, N)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	ANOVA
Weight-for-length z-score (mean,	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	ANOVA

SD, N)							
MUAC z-score (mean, SD, N)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	ANOVA
Head circumference z-score (mean, SD, N)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)	ANOVA
Incidence of severe stunting at 6 months of age (percentage)	xxx / xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	Fisher's exact test
Incidence of moderate and severe stunting at 6 months of age (percentage)	xxx / xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	Fisher's exact test
Blood hemoglobin concentration g/dl (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Proportion of participants with anaemia (percentage)	xxx / xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	Chi-squared
ZPP concentration µg/g (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
ZPP concentration >45 (percentage)	xxx / xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	xxx/ xxx (xx%)	Chi-squared

Table 1b Other baseline characteristics to be assessed

Variable	**Control**	**10g milk LNS**	**20g milk LNS**	**20g milk-free LNS**	**40g milk LNS**	**40g milk-free LNS**	**Test**
Maternal Age, years (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Maternal height, cm (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Maternal Weight ,kg (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Maternal BMI (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Maternal MUAC, cm (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Maternal education, years (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Paternal age, years (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Paternal education, years (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	ANOVA
Total number of persons in the household (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	Kruskal-Wallis test
Total number of children below 5 years of age in the household (mean, SD, N)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	Kruskal-Wallis test
Proportion with malaria parasiteamia at enrolment, number (percentage)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	xxx / xxx (xx%)	Chi-squared

Table 2 Anthropometric outcome changes during and up to 12 months of intervention

Variable	**Control**	**10g milk LNS**	**20g milk LNS**	**20g milk-free LNS**	**40g milk LNS**	**40g milk-free LNS**
Mean (SD) change in length-for-age z-score mean, Z-score units	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Difference (95% CI) in means between the indicated intervention and the control group		xxx (xx to xx)	xxx (xx to xx)	xxx (xx to xx)	xxx (xx to xx)	xxx (xx to xx)
Mean (SD) change in length, cm	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)	x.xx (x.xx)
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx
Difference (95% CI) in means between the indicated intervention and the control group		xxx (xx to xx)	xxx (xx to xx)	xxx (xx to xx)	xxx (xx to xx)	xxx (xx to xx)

Table 3 Regression results of the effects by the milk-containing and milk-free LNS

	Model: $\hat{y}_i = b_0 + b_1 D_i + b_2 S_i$			**Model:** $\hat{y}_i = b_0 + b_1 D_i + b_2 S_i + b_3 (D_i \times S_i)$		
Variable	**Coefficient**	**90 % CI**	**P-value**	**Coefficient**	**90 % CI**	**P-value**
Constant (b_0)	xx.xx	xx.xx to xx.xx	x.xxx	xx.xx	xx.xx to xx.xx	x.xxx
Difference in mean change in LAZ in 40g dose LNS compared to 20g dose LNS (b_1)	xx.xx	xx.xx to xx.xx	x.xxx	xx.xx	xx.xx to xx.xx	x.xxx
Difference in mean change in LAZ in milk-free LNS compared to milk-containing LNS in 20 g group (b_2)	xx.xx	xx.xx to xx.xx	x.xxx	xx.xx	xx.xx to xx.xx	x.xxx
Difference in mean change in LAZ in milk-free LNS compared to milk-containing LNS in 40 g group ($b_2 + b_3$)				xx.xx	xx.xx to xx.xx	x.xxx

Table 4 Incidence of SAEs by study group

	Intervention group						
Intervention group	**Control**	**10g milk LNS**	**20g milk LNS**	**20g milk-free LNS**	**40g milk LNS**	**40g milk-free LNS**	**P-value**
Number of participants	xxx	xxx	xxx	xxx	xxx	xxx	
Number of participants with at least one episode of SAE (% with SAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx.xxx
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	
Risk ratio (95% CI) between the indicated intervention and the control group	1.00 (ref)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	
Number of participants with fatal event (% with SAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx.xxx
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	
Risk ratio (95% CI) between the indicated intervention and the control group	1.00 (ref)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	
Number of participants with life threatening event (% with SAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx.xxx
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	

Risk ratio (95% CI) between the indicated intervention and the control group	1.00 (ref)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	
Number of participants with hospitalization (% with SAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx.xxx
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	
Risk ratio (95% CI) between the indicated intervention and the control group	1.00 (ref)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	
Number of participants with significant disability (% with SAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx.xxx
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	
Risk ratio (95% CI) between the indicated intervention and the control group	1.00 (ref)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	
Number of participants with other SAE (% with SAE)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx.xxx
Raw p-value for intervention compared to control		x.xxx	x.xxx	x.xxx	x.xxx	x.xxx	
Risk ratio (95% CI) between the indicated intervention and the control group	1.00 (ref)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	x.xx (xx to xx)	