Efficacy of lipid-based nutrient supplements (LNS) for pregnant and lactating women and their infants (iLiNS DYAD-Ghana and iLiNS DYAD-Malawi)

Statistical Analysis Plan

Effect on breastfeeding practices from birth to six months (Date 15 Oct 2014)

Contents

1. Version history

Version number	Version date	Prepared by	Description of the completed editions
01.0	XX.XX.2014	Arimond, Dewey Peerson	Original document added 15 Oct 2014

2. Overview and study objectives

The analysis presented here is nested within a pre-existing iLiNS-DYAD-G and iLiNS-DYAD-M analysis plans for primary and other secondary outcomes. Refer to the main analysis plans for: inclusion and exclusion criteria for the trial; data cleaning protocols; procedures for breaking code; and procedures for modifying this protocol.

The main objective of data collection related to breastfeeding practices before six months of age is to compare neonatal practices and exclusive and predominant breastfeeding practices across intervention groups. Analysis will be within (not across) site.

The intervention could impact practices through affecting the mother's health and/or her perceptions of her own: health; nutritional status; or breast milk quality. All of these could impact her perception of her ability to exclusively or predominantly breastfeed her infant up to 6 months of age. The intervention could also impact breastfeeding practices through impacts on the infant (appetite, vigor and/or demand for breastfeeding).

IYCF practices we will compare across groups include: early breastfeeding practices (early initiation, use of prelacteals); exclusive and predominant breastfeeding for infants under 6 mo of age

Specific objectives of analysis

1.1 Primary objective

To compare specified breastfeeding practices up to 6 months of age across intervention groups.

1.2 Secondary objective

To provide additional descriptive data on breastfeeding practices to contextualize results, and to aid readers in comparing to other settings.

3. Hypotheses to be tested

Provision of LNS to mothers during pregnancy will increase early initiation of breastfeeding and decrease use of prelacteals during the first week after birth.

Provision of LNS to mothers during pregnancy and the first six months will increase exclusive and predominant breastfeeding during the first six months, compared to the IFA group.

4. Description of breastfeeding outcome variables, infants under 6 months

All outcomes are based on maternal recall of practices in response to structured survey questions.

Planned timing of outcome assessment:

Ghana

Early breastfeeding practices were assessed via survey within 1-2 days of birth (recorded on child anthropometry form) and/or on day 8 or later (recorded on "delivery details" form). Exclusive and predominant breastfeeding were assessed based on monthly visits at ~1-5 months of age (allowed up to ± 1 week of the planned visit date). In addition, data from later time points (at ~6 mo and ~9 mo) will be used for survival analyses (see outcomes, below).

Malawi

Early breastfeeding practices were assessed via survey either immediately after delivery (newborn details questionnaire; late collection was allowed for this form) and/or in a home visit with target timing of 7 days (± 7 days) after birth (postnatal care practices questionnaire). Exclusive and predominant breastfeeding were assessed based on four-weekly visits at 4, 8, 12, 16, 20, and 24 weeks (allowed up to ± 1 week of the planned visit date). In addition, data from later time points (at ~6 mo and ~9 mo) will be used for survival analyses.

Outcomes:

The original intention was to create summary variables for exclusive and predominant breastfeeding across time, to better reflect the desired practices since birth. However, this results in substantial loss of sample size in both sites and given the high proportion of missing data (59%) some outcomes will not be constructed for Malawi; several cross-sectional outcomes have been added (#3-8 below).

1. Infant breastfed immediately or within 1 hr[1] (%)
2. Infant not fed any prelacteal[2] in ~ first week (%)
3. Exclusive breastfeeding[3] at 16 weeks (Malawi) or 4 months (Ghana) (%)
4. Predominant breastfeeding at 16 weeks (Malawi) or 4 months (Ghana) (%)
5. Exclusive breastfeeding at 20 weeks (Malawi) or 5 months (Ghana) (%)
6. Predominant breastfeeding at 20 weeks (Malawi) or 5 months (Ghana) (%)
7. Exclusive breastfeeding at 24 weeks (Malawi) (%)
8. Predominant breastfeeding at 24 weeks (Malawi) (%)
9. Mean or median # time points w/exclusive breastfeeding (Ghana only)
10. Mean or median # time points w/predominant breastfeeding (Ghana only)
11. Exclusively breastfed at all 5 time points (%, Ghana only)
12. Predominantly breastfed at all 5 time points (%, Ghana only)
13. Age at first time point not reported to be exclusively breastfed (survival analysis)
14. Age at first time point not reported to be either exclusively or predominantly breastfed (survival analysis)

5. Approach to analysis and exclusions specific to this analysis

All tests will be two-sided, at 5% level of significance.

[1] We considered analyzing also for breastfeeding within the first 24 hours but there is little variability.

[2] The definition of prelacteals was strict; any non-breastmilk liquid or food, regardless of quantity, was considered a prelacteals (e.g in Ghana, infants (usually male) may be given a drop of lemon or lime juice; we classified this as a prelacteals).

[3] In Ghana, the gripe water is sold in sealed bottles, is recommended by and sometimes sold by clinic nurses, and is generally given in very small quantities. While we did consider this a prelacteal, for definition of exclusive breastfeeding, after consultation with the local team, given both the very small volume and the low likelihood of contamination of gripe water, we allowed gripe water under exclusive breastfeeding (i.e., treated as a "medicine"). We also allowed drops of lemon/lime juice, but note this was given in only five instances across all data collection time points (~1-5 mo) used to assess exclusive breastfeeding. In Malawi the opposite decision was taken, and gripe water was not allowed under exclusive breastfeeding because unlike in Ghana, the source, ingredients, quantity and hygiene of gripe water are highly variable. On the questionnaire, it was grouped with water and sugar water and cannot be separated.

Since varying numbers of observations are available depending on the time point (i.e., there were a substantial number of missed visits), sample sizes by group will be reported for each time point. If specific outcome variables are missing for more than 10% of infants (with denominator being total records available for the time point) we will report the number of observations used per specific outcome analysis.

Analysis will be in the first place by intention-to-treat. Data on subjects who were lost to follow-up (either temporarily or permanently) will be included in the analysis for all time points where data are available. This will be followed by a per protocol analysis, with "per protocol" as defined in the main trial analysis plans.

Data available in the DYAD-Ghana trial are divided into three "periods" based on their relationship to an error in allocation of treatments. Women in "period 1" received the same supplement throughout pregnancy, though it was not the intended supplement (reversal of MMN and IFA groups); women in "period 2" received the incorrect supplement at enrollment, but started receiving the intended supplement at some point during the pregnancy; women in "period 3" received the correct supplement throughout pregnancy and lactation. At no point was LNS confused with the two tablets (IFA and MMN).

Questions on neonatal practices were captured at two time points to minimize missing data; data will be taken at from the earliest time point available (for example, in Ghana, data on the delivery details form will be used only if the newborn anthropometry form is missing or incomplete).

For visits at 4 weeks of age and older, observations more than 14 days from the median age per visit will be excluded from all analyses (median age was very close to target age for these time points in each site).

Twins are excluded from all analyses of breastfeeding outcomes under 6 months of age.

6. Statistical methods

5.1 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).

5.2 Background characteristics

Selected background characteristics will be examined by group for analysis samples.

5.3 Analysis of the effect of the intervention

General comments:

Analysis of the effect of the intervention will follow these steps:

a. In Ghana only, we will test group-by-period interactions for each outcome. In the absence of group-by-period interactions, observations from participants in all periods will be included in the analysis, and analysis will be performed both for groups as allocated (reflecting the supplement received during early lactation up to six months post-partum) and for groups based on first supplement received. If there are significant group-by-period interactions for a specified outcome, period 3 data only will be used for that outcome.

b. In each site, we will assess pre-specified covariates (see below) for relationship to each outcome.

c. We will test the null hypothesis of no difference among the three treatment groups using ANCOVA or logistic regression, with and without controlling for significant covariates.

d. If the global null hypothesis is rejected at 0.05 level for any outcome, then we will perform post-hoc pairwise comparisons of all three groups using appropriate adjustments for multiple comparisons to examine contrasts of interest.

e. The effects of potential effect modifiers will be assessed with an interaction term in the ANCOVA or logistic regression model. Each interaction will be assessed separately, in models including all significant covariates.

f. Significant interactions ($p < 0.10$) 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.

g. Confidence intervals will be adjusted for multiple comparisons.

5.5 Covariates in main effects models

In theory, a variety of community-, household-, maternal-, and child-level characteristics could affect child feeding practices independently of the intervention. Data are available for the covariates listed below.

All covariates are as measured at baseline, with the exception of season, and child sex and age. Season of measurement is included in models for outcomes 3-8 as it is conceptualized to impact ease of exclusive/predominant breastfeeding through impacting women's workload. Since child age at each visit can vary (see exclusions above) and since feeding practices change rapidly in early infancy, child age at time of measure will be included in models for cross-sectional outcomes numbers 3-8.

Before making final decisions on inclusion of covariates, completeness of data for the covariates will be considered and covariates will be excluded if loss of sample size is judged too large.

- Enrollment site (Malawi only)
- Season of measurement (cross-sectional outcomes 3-8 only)
- Characteristics of households
    - Baseline HH asset score
    - Baseline HH food security (HFIA score)
- Characteristics of mother
    - BMI[4]
    - Age
    - Parity (dichotomous – any previous live birth, or none)
    - Education
    - HIV status (Malawi only)
- Child's characteristics
    - Child age (cross-sectional outcomes 3-8 only)
    - Child sex

5.6 List of potential effect modifiers to be examined

With the exception of study site and child age, the covariates identified will also be evaluated for their potential to interact with intervention group.

[4] Predicted BMI at 13.7 wk of gestation, for Malawi; BMI at enrollment for Ghana, because baseline BMI was not related to gestational age at enrollment (R-squared = 0.007)

7. Design of tables and figures

The following tables and example figures will be examined by the manuscript writing group:

Table 1. Background characteristics of study participants

Table 2. Breastfeeding practices, by intervention group

Figure 1. Participant flow

Additional figures to illustrate results from survival analysis, and, as needed, to illustrate interactions.

Table 1. Example table for background characteristics of study participants in analysis sub-sample (possibly, separate tables per outcome)[a,b]

		IFA N = XXX	MMN N = XXX	LNS N = XXX	p-value[c]
Site (%)					
	Lungwena				
	Malindi				
	Mangochi				
Season of measure (%)					
	(Describe)				
	(Describe)				
	Etc.				
Asset index (mean)					
HFIA score (mean)					
Mother's BMI					
Mother's age (y)					
Primigravid at enrollment (%)					
Mother's education (y)					
Mother HIV positive (%)					
Child male (%)					
Child age at *[X visit]* (mo)					

[a] *[Will evaluate how different the sub-samples comparisons are for various outcomes, and decide how to handle in presenting results. If the comparisons are similar across outcomes, we will select one to present and note that others are similar.]*

[b] IFA=iron folic acid group (standard care); MMN=multiple micronutrient group; LNS=lipid-based nutrient supplement group.

[c] Comparison between intervention groups; p-value for ANOVA (continuous and quasi-continuous variables) or chi-square test (categorical variables).

Table 2. Breastfeeding practices, by intervention group

	N[a]	(missing)	IFA[b]	MMN	LNS	All	P-value[c]
Infant breastfed immediately or within 1 hr (%)							
Infant not fed any prelacteal in ~ first week (%)							
Exclusive breastfeeding at 16 weeks (Malawi) or 4 months (Ghana) (%)							
Predominant breastfeeding at 16 weeks (Malawi) or 4 months (Ghana) (%)							
Exclusive breastfeeding at 20 weeks (Malawi) or 5 months (Ghana) (%)							
Predominant breastfeeding at 20 weeks (Malawi) or 5 months (Ghana) (%)							
Exclusive breastfeeding at 24 weeks (Malawi) (%)							
Predominant breastfeeding at 24 weeks (Malawi) (%)							
Mean or median # time points w/exclusive breastfeeding (Ghana only)							
Mean or median # time points w/predominant breastfeeding (Ghana only)							
Exclusively breastfed at all 5 time points (%, Ghana only)							
Predominantly breastfed at all 5 time points (%, Ghana only)							

[a] Number of infants not permanently lost to follow-up at time of measure for each outcome, and at final time of measure for outcomes summarized across time.

[b] IFA=iron folic acid group (standard care); MMN=multiple micronutrient group; LNS=lipid-based nutrient supplement group.

[c] Values presented are unadjusted means (SD) or medians (I-Q ranges), or prevalence. Decision on presenting means or medians will be made after examination of distributions. Statistical tests are for adjusted analyses; analysis of covariance and logistic regression, controlling for…..