Healthy Mums, Healthy Babies in Ethiopia: a Cluster-randomized Trial to Evaluate the Programme Effectiveness of a Multiple Micronutrient Supplement Delivered to Pregnant Women Through Routine Antenatal Care to Improve Newborn Birthweight

Statistical Analysis Plan

Version 0.5 dated 21st March 2024

Final version approved by:

Name	Role	Signature	Date

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Name	Role	Signature	Date

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Version Number	Effective Date	Reason for Change	Change approved by
0.1	19th September 2022	First version	
0.3	15th January 2024	New survey design	
0.4	1st February 2024	Internal review	
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1 Background

At the request of CIFF and the Ethiopian Federal Ministry of Health (MoH), the EPHI/LSHTM evaluation team have been asked to design and implement a three-part programme effectiveness evaluation of the 'Healthy Mums, Healthy Babies' investment in Ethiopia which considers a switch in routine antenatal care policy to include multiple micronutrient supplementation (MMS) instead of iron and folic acid (IFA) supplements. A test of scale implementation programme will take place in 21 woreda during 2022-24. The EPHI/LSHTM evaluation will comprise of three components:

1. Cluster randomised controlled trial to examine health impacts (birth weight)
2. Process evaluation to understand implementation
3. Cost and cost-effectiveness evaluation to understand costs

This document details evaluation component 1 only.

2 Hypothesis and objectives

2.1 Aim

To evaluate the programme effectiveness of providing MMS as part of routine antenatal care, relative to providing IFA, on birthweight.

2.2 Hypothesis

Babies born in health facilities to mothers living in areas where MMS is implemented have mean birthweights at least 35g higher than babies born to mothers who give birth in health facilities where standard antenatal IFA supplementation is provided.

2.3 Primary objective(s)

To estimate the effect of MMS implementation on the mean birthweight of babies born in government health facilities to women living in areas where MMS is implemented, relative to the mean birthweight of babies born in government health facilities to women living in areas where standard antenatal IFA supplementation is implemented.

2.4 Secondary objective(s)

To estimate the effect of MMS on mean birthweight according to levels of receipt and use of MMS and IFA.

3 Methods

3.1 Protocol version

This analysis plan is based on the current version of the version 3 dated 28th September 2023.

3.2 Study design

The overall study design is built around a two-arm, facility-based, cluster randomized trial with district as the unit of randomization (the cluster). Districts are randomized to either a comparison arm that continues to deliver iron-folic acid supplementation (IFA) as part of the standard antenatal care package, or to an intervention arm where IFA is removed from the standard antenatal care package and replaced with multi-micronutrient supplementation (MMS).

The original data collection plan was for pre- and post-intervention facility-based survey. Due to changes in implementation plans, the data collection plan has been adapted to be based on a census of all births at the facility level over 24 months, to collect birthweight data and additional data to address secondary objectives.

3.3 Randomisation

A list of 42 purposively identified districts from five regions of Ethiopia was drawn up by the ministry of health and UNICEF. Districts were randomised in a 1:1 ratio to the intervention and comparison groups, with the randomisation stratified by region to ensure a regional balance in the treatment groups. Within each of the strata, districts were each assigned a random number and the district list ordered by that random number, from lowest to highest. One half of the districts - those with the lowest random numbers - were assigned to intervention and the remaining districts assigned to comparison.

3.4 Outcomes

3.4.1 Primary outcome

Birthweight measured as part of routine maternity care in enrolled facilities will be measured in intervention and comparison areas.

Digital scales are provided to facilities for this purpose, replacing manual scales. The study supervision team will work with midwives to ensure training in appropriate use of digital scales, accurate recording of birthweight in grammes to four digits, and continuous quality control measures including scale calibration.

3.4.2 Secondary outcomes

There are no secondary outcomes to be considered in the analysis.

3.4.3 Timing of assessment of outcomes

Birthweights will be measured continuously in health facilities over the duration of the evaluation.

3.5 Sample size

At the outset we estimated that, assuming an intraclass correlation coefficient (ICC) of 0.003, a trial involving 21 districts in the intervention arm and 21 districts in the comparison arm would provide 80% power to detect a 35g increase in mean birthweights over 24 months, assuming a pre-intervention mean birthweight of 3000g with a standard deviation of 500g ([1] – [4]), if 305

birthweights were observed in each district (a total of 12,810 birthweights at baseline and at endline, equating to a study design effect of 2.0).

Observing at least 15 births in every cluster each month, i.e. 15,120 birthweights total, would allow us to detect the same effect at the larger ICC of 0.0055 assuming a linearly increasing difference in birthweights between groups with a between-month autocorrelation of cluster-level outcomes of 0.9.

4 Trial datasets

4.1 Levels of analysis

Statistical analysis will be conducted at the individual mother-child dyad level, with appropriate adjustment for clustering.

4.2 Intention-to-treat and per-protocol datasets

The intention-to-treat dataset will include participants grouped according to their treatment allocation regardless of their uptake of the intervention.

The per-protocol dataset will be restricted to women who self-report to have received either IFA or MMS.

5 Study population

5.1 Trial flowchart

Participants included in the analysis grouped by health facility will be described according to CONSORT 2010 guidelines.

5.2 Eligibility

Study health facilities are any health centre or hospital in study woreda with at least 15 births per month in October to December 2022 according to the DHIS-2 and confirmed through facility registers. In woreda where there were no facilities with at least 15 births per month, all facilities were included up to a maximum of 5 per woreda.

The number of participants screened for eligibility will be presented. The newborn birth weight for all women who give birth in study health facilities during the continuous data collection period are potentially eligible and will be documented, including the following potential reasons for exclusion:

- Women who do not give consent for birth weight data to be recorded;
- Women who experience a stillbirth;
- Women who experience an emergency health event.

Data on multiple births will be collected with the primary analysis restricted to singleton live births.

5.3 Demographic characteristics

The characteristics of participants included in the analysis will be summarised according to treatment group. Descriptive statistics will include counts and proportions of categorical variables, and means with standard deviations or medians and interquartile ranges for continuous variables. No statistical tests to compare groups according to demographic characteristics will be conducted.

6 Statistical analysis

6.1 Statistical software

Statistical analysis will be conducted using Stata version 17.

6.2 Statistical methods

6.2.1 Analysis of primary outcomes

The primary analysis will be conducted on the intention-to-treat dataset. We will use a mixed effects generalised linear model with a Gaussian link with cluster-level random effects to estimate the overall mean difference in birthweight over the whole duration of the evaluation comparing MMS versus standard care (IFA) clusters with the 95% confidence intervals..

6.2.2 Secondary analysis

Mean birthweights at cluster level over time in each of the two arms will be plotted to visually examine trends over the period of evaluation and seasonal patterns (i.e. periods of food plenty vs. scarcity). Any observed trends in birthweight over time will be explored by further fitting interactions e.g., between treatment group and time or treatment group and season, to explore any differences in treatment effect over time or across season, respectively.

6.2.3 Subgroup analysis

The effect of the intervention among women who (i) received it within the first 24 weeks of pregnancy and who (ii) self-report consuming at least 90 tablets during pregnancy will also be assessed.

6.2.4 Analysis of safety of the intervention

Tabulation of adverse events frequency and proportions will be conducted according to treatment arm. No formal statistical testing of between-group differences will be done.

6.3 Statistical and analytical issues

6.3.1 Adjustment for covariates

Unadjusted effect estimates will be reported. Additionally, estimates adjusting for gestational age, sex, and parity, will be reported. Additional exploratory analyses will be conducted to control for any baseline characteristics that appear to be imbalanced between arms.

6.3.2 Missing data

If a large amount of missing data occurred and there appeared to be a difference in missingness between arms, in addition to exploring the reasons for differences in missingness we shall consider inverse probability weighting of observed data in our analyses.

6.3.3 Outliers

Unusual and extreme values of observations will be queried, and only included in the analysis if found to be correct.

6.3.4 Sensitivity analysis

Sensitivity analyses may be conducted with outliers excluded.

6.4 Data management

Data will be collected using in ODK using handheld computers (PDAs) during the surveys, and data from the facility delivery registers will be extracted into paper questionnaires. Data will be will be checked for completeness and consistency. Internal and external consistency of collected data will be examined, for example, through checking the data against information held in the facility registers and re-interviewing a subset of mothers. The PDAs and questionnaires will then be transferred to the EPHI central data processing unit where entry of the questionnaire data will be conducted and data in the PDAs will be extracted into Stata. Additional data quality checks and further cleaning will be conducted, including re-checking missing values, outliers and any other errors identified against raw data. Data cleaning will be documented using .do files in Stata. EPHI will maintain raw locked files of original datasets from which copies for further cleaning and processing will be done. [Data management team to add]

6.5 Data safety and monitoring

An independent Data Safety and Monitoring Board (DSMB) will be established before the start of the trial. The DSMB will meet and review, with strict confidence, the trial data approximately yearly for the duration of the trial. The Chair of the DSMB may also request additional meetings/analyses. No formal interim analysis of the data is planned. Information on the rate of stillbirths over time will be collected and monitored. Observations of an increase in the number of stillbirths will be reported to the DSMB.

7 References

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4. Endalamaw A et al. Italian Journal of Pediatrics https://doi.org/10.1186/s13052-018-0586-6