Efficacy of a food targeting the microbiota for a sustained recovery of children with uncomplicated acute malnutrition

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Statistical analysis plan

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Background

Acute malnutrition defined by wasting (weight-for-height below 2 standard deviations of the WHO growth standards), remains a major public health problem. An estimated 7.3% (50 million) of all children under five are affected globally each year, contributing to approximately half of all annual childhood deaths. One of the sustainable development goals (SDG) is to end all forms of malnutrition, including achieving by 2025, the world Health Assembly (WHA) target to reduce the prevalence of wasting in children under five years of age to less than 5% and maintain this reduction. However, since the targets were adopted, the proportion of wasted children has remained almost unchanged (7.4% in 2015 and 6.9% in 2019). Therefore, progress in reducing acute malnutrition needs to accelerate globally if it is to meet this target.

A proof-of-principle trial using one of the formulations (MDCF-2) was conducted among Bangladeshi MAM children and showed promising results regarding repairs of the microbiota (which composition resembled to that of aged matched healthy children). These inspiring findings need confirmation from different geographic areas and populations and further assessment of this therapeutic approach for treating childhood undernutrition. The present trail will be conducted in Burkina Faso and Niger to evaluate the effectiveness of the MDCF-2 compared to RUSF and RUTF in community management of children suffering from acute malnutrition.

Study objectives

The primary objectives of this study are that providing:

- A microbiota-directed food supplement leads to higher sustained recovery rate relative to standard treatments of acute uncomplicated malnutrition.
- The microbiota-directed food supplement is cost-effective compared standard treatments of acute uncomplicated malnutrition.

Study Methods

Study area and population

The trial will be conducted in three (3) health districts located in the Centre-Ouest and Nord regions of Burkina Faso. In these purposely selected districts, 32 health center catchment areas are selected based on the case admission rate, accessibility and distance to the health center to ensure that subjects will attend follow up visit in the health centers. Children aged 6 to 23 months presenting uncomplicated acute malnutrition with their mothers constitute the study population.

Study design

This is a stratified and individually randomized efficacy trial assessing the effect of microbiota-directed food supplement recovery and sustained recovery of malnourished children.

Children participating in the trial will be supplemented and followed at regular intervals (one week for SAM and two weeks for MAM children) up the twelfth weeks (or up to recovery). They are subsequently invited to a monthly visit up to the twenty-fourth week (Figure 1).

The study protocol is approved by the national ethics committee for health research, and will be registered on clinicaltrials.gov. Written informed consent will be sought and obtained before including any participant in the study.

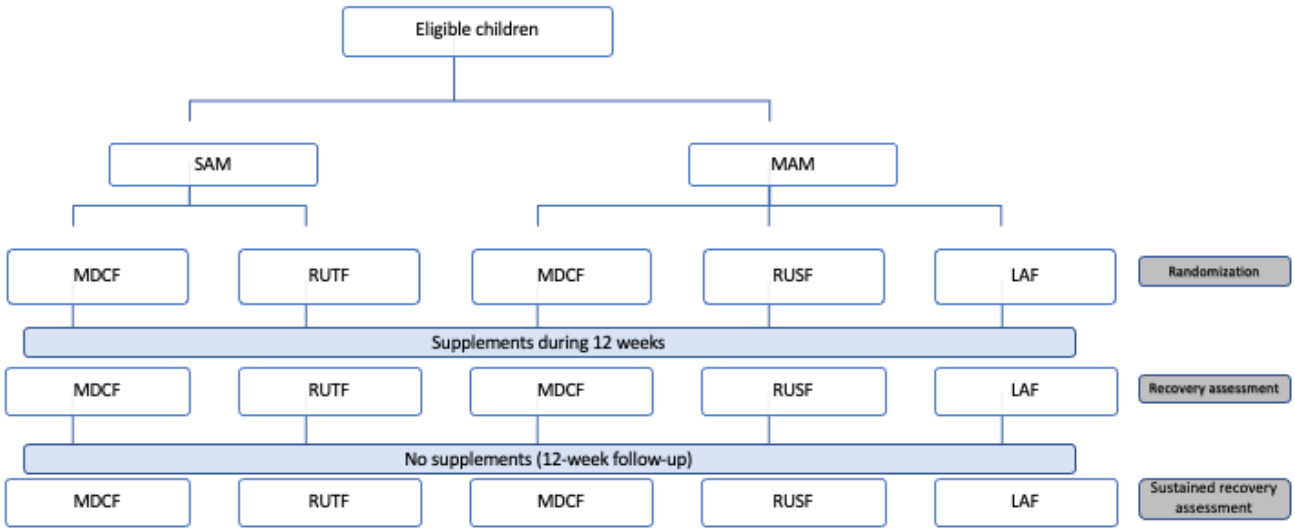

Figure 1 Study design of the randomized controlled trial.

Study eligibility and recruitment

A census will be conducted in the villages of 32 health center catchment areas, by community workers who routinely visit and screen under 5-year-old children malnutrition using MUAC tape. Children with MUAC < 125 mm are referred to the health centers for confirmation and inclusion to CMAM program. Children residing in the areas selected for the study and presenting to the primary health center will be invited to participate in the study.

Inclusion criteria:

- Age between 6 and 23 months of age at enrollment,
- moderate wasting (WHZ < -2 and ≥ -3 or MUAC < 125 mm and ≥ 115mm) or severe wasting: WLZ < -3 or MUAC < 115 mm with respect to WHO Child Growth Standards (Ref WHO 2006),

Exclusion criteria:

- bilateral pitting edema,
- not eating/lack of appetite,
- current illness medical complications requiring inpatient treatment,
- presence of any congenital abnormality or underlying chronic disease that may affect growth or risk of infection, known contraindication / hypersensitivity / allergy to MDCF of RUSF ingredients (chickpea flour, soy flour, banana, peanut),
- recently (<2 months) or enrolled in a nutrition program,
- residence outside the study area.

Eligible participants will be allocated into one of the study groups in a ratio of 1:1:1 for MAM and 1:1 for SAM. The randomization scheme will be generated by a computer program in permuted blocks of 4, stratified by site. The study is not blinded since the three types of supplements will be visibly different for mothers, project staff and data collectors.

Study intervention

Weekly visits at the health center will be scheduled for SAM children (bi-weekly for MAM) for anthropometric measurements and supplements distribution. All anthropometric measurements will be done in duplicate. Each mother will receive the quantity of supplements for home consumption corresponding to her child's weight and the number of days until the next visit. At 12 weeks form the inclusion, the supplementation is stopped and children assessed for programmatic recovery.

From that moment onwards children who recovered will be invited for monthly until the child reaches 23 months age. Those recovering before weeks will also stop the supplementation and start the monthly visit from the twelfth week.

Controls

Level of blinding

The allocation to intervention or control study group is not blinded from the participants. Data collection and outcome assessment are done at the health center by the project and health facility personnel.

Method of treatment assignment/randomization

We will apply a stratified permuted block randomization schedule to allocate children to intervention or control group in both degree of malnutrition. Per health center (=stratum) women will be individually randomly in permuted blocks of xxx so that per block equal numbers. The double random sequence will be generated before the start of the study using Stata 15.1 (Stata Corp, Texas) by a research analyst who is not part of the study team and who is unaware of the study's objectives and procedures. A time coded Stata log-file is available upon request after the completion of the study to assess the randomization sequence generation.
The allocation group code is placed in a sealed opaque envelope by a person not participating in the implementation of the trial. When allocating a participant, the trial nurse will open the next sealed envelope and transmit the assignment code. The person responsible of the supplementation logistics delivers the supplements to the health personnel in the health centers.

Study outcomes

The primary study outcomes of the efficacy trial are:

- Recovery rate at 12 weeks form inclusion (WHZ of MUAC calculated using the 2006 WHO growth reference)
- Sustained recovery rate at 24 weeks (WHZ of MUAC calculated using the 2006 WHO growth reference)

Secondary study outcomes are shown in Table 3.

Table 3 Secondary study outcomes at maternal, newborn and child level

Outcome	Indicator	Timepoint	
		12 weeks	24 weeks
WHZ	Mean change over 12 weeks of supplementation	x	
LAZ	Mean change over 12 weeks of supplementation	x	
WAZ	Mean change over 12 weeks of supplementation	x	
Time to recovery	Mean number of days to recovery	x	
Relapse rate	% Children presenting inclusion criteria within 3 months following discharge		x
Non-response	% Children not gaining weight after 2 weeks or a WHZ<-2 SD after 8 weeks	x	
Default rate	% Children absent or refusing food during 3 consecutive weeks	x	
Mortality	Number of deaths during follow up	x	x
Hospitalization	Mean number of illnesses which required hospitalization	x	x
Compliance	Mean number of sachets of supplement consumed	x	
Cost-effectiveness	Incremental cost per child treated	x	
Cost-effectiveness	incremental cost per SAM case averted	x	
Cost-effectiveness	The incremental cost-effectiveness ratio (ICER)	x	

Analyses

Baseline characteristics

For all variables measured, the available values at enrollment, i.e. before the start of the intervention, will be considered as baseline characteristics. Following CONSORT guidelines, no statistical tests will be conducted comparing baseline characteristics between study arms. Differences in baseline characteristics will be appreciated by comparing values of means and proportions.

The presentation of baseline characteristics will be done as follows:

- Categorical variables: frequencies and percentages, as appropriate. Percentages will be calculated based on the number of participants for whom data are available.
- Continuous variables: mean and SD or median and interquartile range, as appropriate.
- Where data for certain participants are missing, the number of participants included in the analysis will be indicated.

Efficacy

The outcomes are measured at two timepoints and the analysis will be by intention-to-treat, according to pre-specified eligibility criteria. For binary outcomes, we will calculate risk ratios that will be analyzed using log-binomial regression models. In the unlikely event that the latter models do not converge, Poisson regression models with robust estimation of standard errors will be used. The analyses will be adjusted for prognostic variables (listed in **table 4**) that differ at baseline between study groups. These factors were previously reported to be associated recovery. This adjustment strategy will account for baseline imbalances and will increase statistical power by reducing variance. All analyses will be adjusted for health center (fixed effect) to reflect the stratified sampling design. Statistical tests will be one-sided for outcomes assessed at 12 weeks, and two-sided for those assessed at 24 weeks, at the 5% level of significance. Unless specified otherwise, continuous outcomes measured at one time point will be analyzed using ordinary least squares regression, using the same adjustment variables.

Table 4. Prognostic factors of study outcomes

Factors
Age
Admission weight
Breastfeeding status
Immunization status
Sex

Cost effectiveness

The average cost per Recovered child and child who Sustained recovery per supplement will be calculated and compared for MAM and SAM treatment using the following equations:
- Cost per Recovered Child = (Cost per Enrolled Child)/(% Recovered)
- Cost per Child Who Sustained Recovery= (Cost per Enrolled Child)/(% Recovered *% Sustained Recovery)
Cost and effectiveness of the treatment will be compared using the incremental cost per child treated, recovered child and who child sustained recovery:
- 2x2 for MAM treatment (MDCF vs RUSF, RUSF vs LAF and MDCF vs LAF), and
- MDCF vs RUTF for SAM treatment.