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Microbiome-directed food to promote sustained recovery in children with uncomplicated acute malnutrition: protocol for a randomized controlled trial in Burkina Faso

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Abstract

Background Acute malnutrition still affects millions of children under five years of age globally each year and contributes to approximately half of all annual childhood deaths. A considerable proportion of patients who recover from acute malnutrition experience poor health and nutrition and eventually relapse after they are discharged from community management of acute malnutrition programs. A microbiota-directed complementary food (MDCF) showed a superior effect compared to standard ready-to-use supplementary food (RUSF) in terms of ponderal growth and potential benefit for bacterial taxa that were correlated with weight-for-height z-score (WHZ). This paper describes a protocol for the MDCF phase III trial on a larger African sample for promoting sustained recovery.

Methods This study is an individually controlled open-label phase III trial to determine the efficacy of MDCF on programmatic and sustained recovery compared to standards RUTF and RUSF. Eligible MAM children will be randomly assigned to MDCF or RUSF and those with SAM to MDCF or RUTF. Supplementation and follow-up visits will be performed following national guidelines for acute malnutrition management. Primary outcomes are programmatic recovery at 12 weeks after enrollment and sustained recovery at 12 weeks after recovery. The secondary outcomes included the mean WHZ, weight-for-age z score, height-for-age z score change, average length of stay, nonresponse, failure and dropout.

Discussion The present study is designed to investigate the efficacy of a microbiota-targeted food in treating acute uncomplicated malnutrition and preventing relapses. It will provide evidence as a phase III clinical trial.

Trial registration Clinicaltrials.gov Protocol registration and results system (NCT05586139). Registered on 2022–10–14. https://register.clinicaltrials.gov/.

Keywords Microbiome, Complementary food, Sustained recovery, Acute malnutrition, Relapses

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Background

Acute malnutrition, defined by wasting, remains a major public health problem in developing countries, particularly in Africa. An estimated 7.3% (50 million) of children under five years of age are affected globally each year, contributing to approximately half of all annual childhood deaths [1]. Wasting leads to weakened immunity, susceptibility to long-term developmental delays and an increased risk of death, especially in its most severe form or when combined with stunting [2]. According to the 2019 United Nations Children´s Fund (UNICEF), World Health Organization (WHO) and World Bank estimates, approximately 4.5 million and nearly 1 million children in West African countries are affected by wasting and severe wasting, respectively [3]. According to the 2020 National Nutrition Survey in Burkina Faso, 9.1% of children under the age of 5 suffer from acute malnutrition [4].

One of the sustainable development goals (SDGs) is to address all forms of malnutrition, including by 2025, when the World Health Assembly (WHA) targets reducing the prevalence of wasting in children under five years of age to less than 5% and maintaining this reduction (Target 2.2). However, since the targets were adopted, the proportion of wasted children has remained almost unchanged (7.4% in 2015 and 6.9% in 2019) [5].

Acute malnutrition is classified as moderate or severe based on its severity. These two types of acute malnutrition are managed separately, using different protocols and products. Case definitions for severe acute malnutrition (SAM) in children of this age include low WHZ, low MUAC, and/or nutritional edema. SAM children without complications can be treated as outpatients in their communities using specially formulated food and medication through an approach called community-based management of acute malnutrition (CMAM). For almost two decades, a home-based therapy with ready-to-use therapeutic food (RUTF) for the treatment of uncomplicated SAM has been recommended by UN agencies [6]. Compared with an alternative dietary approach, RUTF has been shown to improve recovery from SAM by 33% [7]. However, there is currently no consensus on the best possible management strategy for moderate acute malnutrition; while some national guidelines suggest the provision of supplementary food products, others recommend nutritional counseling to the caregivers of MAM children. Currently, there are no evidence-based recommendations on the composition of supplementary foods used to treat children with MAM [8]. The food approach used in the management of MAMs predominantly focuses on community-based supplementary feeding (SFP) programs, which provide a variety of supplements [9]. MAM children are generally treated for several weeks using fortified blended flours (FBF) or lipid-based nutrient supplements (LNS) and are discharged after achieving an anthropometric threshold (recovery) or after receiving food for a fixed duration of time.

An emerging body of evidence shows that some children who recover from SAM or MAM go on to experience poor health and nutrition after they are discharged from the CMAM program, including relapse [10, 11]. Relapse occurs when a child's health and nutritional status deteriorate to MAM or SAM after a period of recovery. Systematic reviews on relapse to severe wasting [10] and long-term treatment outcomes [12] reported a proportion of discharged children relapsing to severe wasting ranging from 0 to 37% across timeframes between 1 week and 18 months. In Africa, two studies reported 36% of relapses at 12 months among MAM children successfully treated with LNS (Ref) and 20% of relapses at 6 months following treatment with CSB [13]. A study from Burkina Faso including a population of 90% MAM and 10% SAM reported a relapse rate closer to 15%, despite a high proportion of children lost to follow-up, possibly suggesting an even higher rate of relapse or death [14]. The prevention of relapse is likely to be an important aspect of wasting prevention in general.

Factors associated with the risk of relapses are not fully understood, but low anthropometric measures at admission or at discharge from SFP have been commonly reported [14–16]. Severe malnutrition is often associated with comorbidities, and it is likely that children with low MUAC or low WHZ have additional underlying physiological disturbances that take longer to recover than simple anthropometric recovery. Therefore, evaluations of supplementary feeding programs should assess outcomes beyond improvements in conventional anthropometric indicators to reflect a "healthy" recovery [17, 18].

Although malnutrition has been causally associated with an imbalance in food intake and several poverty-related factors, such as low birth weight, infections, and low socioeconomic status. In addition, the gut microbiota (GM) composition and the gastrointestinal environment have recently been shown to play a central role in its etiology [19]. Changes in microbiota composition marked by increased gut permeability and inflammation [20, 21] have been shown to be involved in the development or maintenance of acute malnutrition [22–24]. Studies have demonstrated changes in the fecal microbiomes of undernourished children [19, 23], particularly their immature configurations, which are similar to those of healthy but chronologically younger children, revealing the link between microbiome immaturity and malnutrition. In addition, the reduced diversity of the microbiome was associated with poor anthropometric indicators [25].

In recent decades, important advances in research on the GM have been made, especially related to its relationship with host physiology. The gut microbiota in the digestive tract plays a role in helping nutrient metabolism

processes, strengthening gut integrity, increasing the immune response, and protecting against pathogens [26]. GM maturation, marked by increased diversity, occurs mainly during the first three years of life [27].

For a long time, it has been demonstrated that food with or without probiotics is able to shape the GM [28], and malnutrition has been associated with the GM composition and the gastrointestinal environment. For instance, differences in the composition and number of observed species in the GM have been found between children with non-edematous SAM and those with edematous SAM [29]. On the other hand, the impact of nutritional interventions on the GM in malnourished children has been demonstrated. In a follow-up study of twin pairs during the first three years of life among Malawian children, treatment with RUTF produced a transient maturation of metabolic functions in the microbiomes of children with Kwashiorkor; the maturation regressed when RUTF was stopped [24]. This suggested a "blocking of maturation" of the gut microbiome in children with malnutrition, which was not found in healthy cotwins from discordant pairs [24].A birth cohort of Bangladeshi children from urban slums was followed for 2 years, and the composition of their GM was analyzed [23]. Based on age-discriminatory bacterial taxa, the authors developed microbiota maturity scores. Compared with their well-nourished peers, children with SAM showed significant GM immaturity, and supplementation with therapeutic foods, including RUTF, partially and temporarily improved GM maturity. On the basis of these observations, the authors developed several therapeutic food supplement (microbiota-directed complementary food, MDCF) prototypes through the screening of combinations of food staples in gnotobiotic mice and piglets [30].

A proof-of-concept trial using one of the formulations (MDCF-2) was conducted among Bangladeshi MAM children and showed promising results regarding the repair of the microbiota (the composition of which resembled that of age-matched healthy children) and the levels of plasma proteins indicative of improved health status [30]. A larger randomized controlled study showed that MDCF-2 produced a superior effect compared to that of a ready-to-use supplementary food (RUSF) with regard to ponderal growth and plasma protein mediators of bone growth and neurodevelopment [31]. These findings need confirmation from different geographic areas and populations and further assessment of this therapeutic approach for treating childhood undernutrition.

In summary, this study hypothesizes that (1) MDCF-2 is not inferior to standard of care (RUTF and RUSF) in the programmatic recovery of uncomplicated acute malnutrition, and (2) MDCF-2 is superior in preventing relapses among children suffering from uncomplicated acute malnutrition.

The primary objective of this study is to determine the efficacy of MDCF on programmatic and sustained recovery compared to standard RUTF for SAM children and compared to standard RUSF for MAM children. The secondary objectives are (1) to assess the safety of MDCF versus RUTF and RUSF based on the incidence of serious adverse events occurring during treatment, and (2) to determine the cost-effectiveness of MDCF compared to RUSF and RUTF in the treatment of uncomplicated acute malnutrition.

Methods/Design

This study aims to test the efficacy of a complementary food targeting the gut microbiota in promoting sustained recovery among children with moderate or severe uncomplicated acute malnutrition in the semiurban health districts of Burkina Faso. The protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guidelines [32].

Study setting

Three health districts located in the *Centre-Ouest*, the *Nord and Centre-Nord* regions of the country were selected as the study sites due to the high admission rates of children in the CMAM program. Burkina Faso is a West African country with a predominantly poor and rural population that is vulnerable to child health and nutrition because of seasonal food insecurity. Undernutrition is common among children under 5 years of age, with approximately 25% of children classified as stunted in the 2020 National Nutrition Survey [4]. The country experienced a reduction of only 2% points in the prevalence of wasting among children between 2009 and 2020 (from 11.3 to 9.1%), making it difficult for the country to achieve SDG 2 ("Eradication of hunger and all forms of malnutrition by 2030").

Each health district is subdivided into primary health facilities called health and social promotion centers (CSPSs). The CSPSs are the first operational care units of the national health system and provide a minimum set of curative, promotional and preventive services. The CSPSs with the highest rates of malnutrition admissions were selected for the study, considering the accessibility and safety of the areas.

Study design

This is an individually randomized controlled trial stratified by the severity of malnutrition to test the efficacy of MDCF in treating uncomplicated acute malnutrition (Fig. 1). Children aged 6–23 months with MAM will be assigned to one of two intervention groups, MDCF or standard RUSF, and those with SAM to one of two intervention groups, MDCF or RUTF. Children will

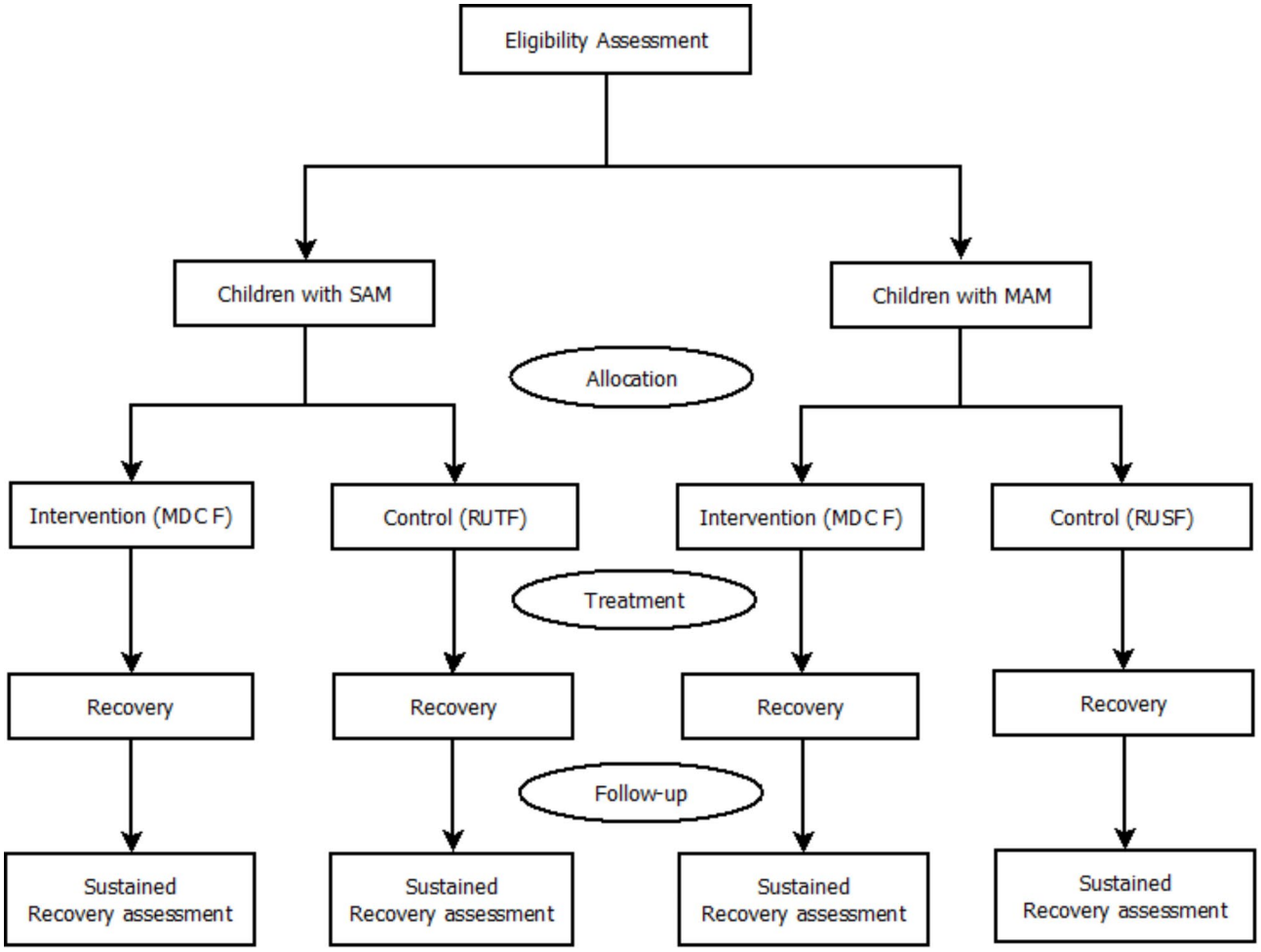

Fig. 1 Study design of the trial: MAM children will be randomly allocated to MDCF or RUSF, and SAM children to MDCF or RUTF. Those recovering before or at week – 12 of enrollment will be followed up for 12 weeks for sustained recover assessment

be followed up weekly for SAM and every biweekly for MAM until recovery or until 12 weeks and then monthly for 12 weeks.

Outcomes and definitions

Primary outcomes.

- Programmatic recovery:
  - MAM: proportion of children who fulfilled the discharge criteria defined by a WHZ ≥ – 2 or a MUAC ≥ 125 mm before or at the end of the 12 weeks after enrollment.
  - SAM: proportion of SAM children who fulfilled the discharge criteria defined by a WHZ ≥ – 2 or a MUAC ≥ 125 mm before or at the end of the 12 weeks after enrollment.
- Sustained recovery:
  - MAM: proportion of children who have a WHZ ≥ – 2 or a MUAC ≥ 125 mm at 12 weeks after discharge.
  - SAM: proportion of children who have a WHZ ≥ – 2 or a MUAC ≥ 125 mm at 12 weeks after discharge.

Secondary outcomes.

- Mean changes in anthropometric indicators, including the WHZ, WAZ, and HAZ, at 12 weeks after admission to the supplementation program and at the end of the follow up;
- Average length of stay: determined by the number of days from admission to programmatic recovery among cured children;
- Dropouts: Absence for 3 consecutive scheduled visits;
- Nonresponse: child with a WHZ < -2 or a MUAC < 125 mm at 12 weeks;

- Failure: Absence of weight gain, assessed at the 3rd consecutive visit; or weight loss since admission to the program, assessed at the 1st visit after admission; or loss of 5% of body weight compared to admission weight;
- Hospitalization: linked to a failure of treatment, a complication or other;
- Serious side effects (see definition in the 'Serious side effects' section);
- Death;
- Treatment adherence: sum of reported sachets/packets of supplements (MDCF and RUSF and RUTF) used divided by the total number of sachets/packets provided;
- Proportions of daily nutritional intake (energy, macronutrients and micronutrients) provided by food supplements (MDCF, RUSF, RUTF) to MAM and SAM children in the trial;
- Cost-effectiveness, as defined by the incremental cost per child cured according to the program and per child cured sustainably.

Sample size

MAM: The sample size calculation is based on the primary outcomes and the two hypotheses. First, MDCF is noninferior to RUSF in terms of the programmatic recovery rate. We considered the results of 2 studies in rural Burkina Faso, the study by Nikiéma et al. [33], which reported a recovery rate of ≈74.5% in MAM children treated with supplementary foods, and the OptiMA proof-of-concept trial in which a simplified protocol of RUTF (different regimen for the treatment of MAM and SAM children) [34]was implemented. The recovery rate ranged from 70.4% for children who had a MUAC < 115 mm to 91.4% for those with a 120 mm < MUAC < 124 mm. With an expected recovery rate of 60% in the RUSF group, a noninferiority margin of 9% (absolute risk difference), and a power of 90% at a one-sided significance level of 0.05, 872 children aged 6–23 months are needed in each study arm. This number was adjusted for a lost to follow-up rate of 10%. Second, MDCF is superior to RUSF in terms of sustained recovery. We set the expected proportion of children who would maintain recovery in the RUSF group at 60%, based on studies in Niger [13] and Malawi [35] reporting the proportion of children who recovered for 12 months without intervention after discharge as 51–63%, respectively. Assuming a 1.25 relative risk of sustainable recovery in the MDCF group, with 90% power, a one-sided significance level of 0.05 and a rate of lost to follow-up of 20%, 1634 children are required per study arm. Hence, the proposed sample size for MAM is 3268 children.

MAS: The calculation of the sample size follows the same principle. First, a noninferiority hypothesis in which MDCF (vs. RUTF) in terms of programmatic recovery at 12 weeks is proposed. We considered an expected recovery rate of 60% in the RUTF group and a noninferiority margin of 6% (absolute risk difference), a one-sided significance level of 0.05, 90% power and 10% of lost to follow-up. A sample of 1622 children aged 6–23 months is needed for each study group. The second hypothesis states the superiority of MDCF over RUTF for sustained recovery; the expected proportion of children sustaining recovery in the RUTF group was set at 60%. Considering a 1.20 relative risk of sustained recovery in the MDCF group, with 90% power and $\alpha = 0.05$, 1479 participants per group are needed. This takes into account a lost to follow-up rate of 20%. The study will enroll 3244 SAM children.

Identification and recruitment of participants

Eligible children will be identified (1) in the community through routine community-based health worker screening activities and (2) by health personnel during maternal and child health care and promotion activities (monitoring of postnatal growth and promotion sessions, vaccination, etc.) or other activities. 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 and exclusion criteria

The inclusion criteria are: age between 6 and 23 months of age at enrollment, moderate wasting (WHZ < -2 and ≥ -3 or MUAC < 125 mm and ≥ 115 mm) or severe wasting (WHZ < -3 or MUAC < 115 mm with respect to the 2006 WHO Child Growth Standards), and signed informed consent from the parent or guardian. Children are excluded if they present any of the following criteria: bilateral pitting edema, not eating/lack of appetite, current illness or medical complications requiring inpatient treatment, presence of any congenital abnormality or underlying chronic disease that may affect growth/response to treatment or risk of infection, known contraindication/hypersensitivity/allergy to MDCF of RUSF ingredients (chickpea flour, soy flour, banana, peanut), recent supplementation (< 2 months) or enrollment in a nutrition program and residence outside the study area.

Participant randomization and blinding

Eligible participants presenting to the CSPS will be allocated to one of the study groups at a ratio of 1:1 for both the MAM and SAM patients. The randomization scheme will be generated by a computer program in permuted blocks stratified by site. A statistician (not involved in the study) will prepare the randomization lists. Randomization numbers will be sealed in opaque envelopes. At each inclusion at the CSPS level, the research staff opened a sealed envelope in a preestablished order to assign the

participant to the study group and so on. The study will not be blinded since the supplements will be visibly different for mothers, project staff and data collectors. However, care will be taken to ensure that project staff performing statistical analyses are not informed of the assignment of children to treatment groups.

Supplement administration

MDCF is a microbiota-directed complementary food formulation (MDCF-2) developed by the ICDDR, B [30], and tested in a POC study involving 12–18-month-old Bangladeshi children with MAM living in an urban slum located in a district of the nation's capital city [31]. The RUSF is the standard Plumpy'Sup, and is already distributed in some regions of Burkina Faso by the WFP through health facilities. In study sites where the WFP is not operating, the supplements will be acquired by the project from *InnoFaso*, a local producer of Plumpy'Sup and Plumpy'Nut in Burkina Faso. RUTF (Plumpy'Nut) will be supplied from the stock of the health facilities (Table 1).

The regimen of food supplements for MAM children is based on the estimated energy intake of 25 kcal/kg/day, which is needed in addition to the requirements of non-malnourished children to support a weight gain of 5 g/kg/day, based on average tissue composition [36]. The baseline energy requirement of infants approximately 2 years of age is 85 kcal/kg/day. MAM children need 25 kcal/kg/day more energy to support a weight gain of 5 g/kg/day during recovery. A total of 20% of this amount is added to account for malabsorption due to enteropathy. In total, the MAM child needs 131 Kcal/kg/day. Half of this amount comes from the home diet, and the remainder (65 kcal/kg/day) comes from the supplement. Considering that 50% of this requirement comes from a child's usual diet, including breast milk, the supplement aims to provide 65 kcal/kg/day. For MAS children, the number of sachets of RUTF to be consumed is guided by national recommendations, following the energy intake recommendation of 170 kcal/kg per day.

Each mother receives a number of sachets based on his child's weight. A supply of supplements (2-wk for MAM and 1-wk for MAS) will be provided along with instructions to feed only to the enrolled child. They will be advised to feed the quantity of supplement required per day and to provide additional complementary foods. Additionally, the supplements and parents/caregivers in all treatment groups will be provided with the usual nutrition counsels prevailing currently in health services, i.e., to continue breastfeeding, to increase diet diversity and to feed frequent snacks. In addition to nutritional supplements, children in all study groups will receive standard of care as per the Burkina Faso National Guidelines.

Table 1 Nutritional composition of food supplements

Composition	MDCF (per 100 g)	Plumpy'Sup (per 100 g)	Plumpy'Nut (per 92 g)
Energy (kcal)	550	540	500
Protein (g)	14,9	12	13
Fat (g)	35,5	35	31
Carbohydrates (g)	-	-	41
Vitamin A, µg	1800	750	736
Vitamin C, mg	68	60	46
Vitamin E, mg	34	17	18
Vitamin B1, mg	0,8	1	0,5
Vitamin B2, mg	2	2,6	1,5
Vitamin B6, mg	0,9	2	0,6
Vitamin B12, µg	3	2,7	1,5
Vitamin K, µg	32	27	14
Niacin (Vitamin B3), mg	7,4	18	4,6
Biotin (Vitamin B7), µg	80	60	55
Folic acid (Vitamin B9), µg	430	256	184
Pantothenic Acid (Vitamin B5), mg	4,3	6,6	2,8
Calcium, mg	326	630	276
Phosphorus, mg	400	600	276
Sodium, mg	10,3	140	139
Potassium, mg	1250	1000	1012
Magnesium, mg	178	170	74
Iron, mg	10,5	11	9,2
Copper, mg	1,7	1,4	1,3
Zinc, mg	12,1	12	10
Selenium µg	30	20	18

Enrollment and follow-up

Enrollment

Before any screening procedure is performed, written informed consent will be obtained from mothers or caregivers. All information related to the study activities and the subject's participation will be given. Consent will be obtained in French or in the mother/caregiver's native language by the study staff. The duration of the study and participation requirements will be explained. The nurse will be trained in how to invite participants without pressure on them. According to the standard procedure, mothers or caregivers will be given a few minutes alone after the consent script is read to consider their decision. As part of the informed consent procedure, interviewers will make it clear that their decision to participate or not will have no effect on their continued benefits of the routine activities in the health center. After providing consent, the mothers/guardians will be interviewed to obtain basic information, including household composition, demographic and socioeconomic status, breastfeeding practices, and history of infant and maternal illness. Medical history questions will include symptoms

of illness in the previous 2 weeks, vaccination status, bed net use, malaria prophylaxis, etc.

Visits schedule

Regular follow-up visits (every week for SAM and every 2 weeks for MAM) will be scheduled until recovery (WHZ ≥-2 or MUAC ≥ 125 mm for two consecutive visits) or up to a maximum of 12 weeks from admission for food distribution and data collection (Table 2). At each visit, anthropometric measurements will be performed; a morbidity questionnaire will be administered before the mother/caregiver receives the supplements for the following period. For the measurement of adherence, mothers will be asked to bring back the empty and unfinished food sachets. A questionnaire will be administered to document any difficulties encountered while feeding the child and the proposed solutions. Questions will also be asked about adverse events observed following the consumption of the supplements.

MAM children who become severely malnourished during supplementation will be referred to the SAM treatment program and treated on either an outpatient or inpatient basis according to the national protocol. These patients will not be randomized again. Children resenting any of the following signs will also be referred for hospital care: weight loss over 3 weeks; stagnation of weight over 4 weeks; appearance of edema; appetite test failure; and clinical complications (fever, hypothermia, severe dehydration, repeated vomiting, severe respiratory distress, chest indrawing, severe pallor with respiratory distress, malaria with signs of severity, abscess or extensive skin lesions, very weak, apathetic or unconscious, or seizures).

Children who have missed their appointments will be visited at home by the community health workers (CHWs) and encouraged to attend health center visits. In case of refusal to continue participation, the follow-up of the child will be stopped. If a child misses two [2] consecutive follow-up visits despite home visits from CHWs or nurses, they will be declared defaulter.

At the end of the 12 weeks, the supplementation will be stopped, and children who have recovered will be invited to a monthly visit for 12 weeks. Mothers will be explained that their child has gained weight and no longer needs food supplements. They will be informed of the importance of maintaining good complementary feeding practices to sustain the weight and health of their children. This includes continuing breastfeeding and providing appropriate nutrient-dense food in quantity and the required number of meals per day. They will also be advised to return to the health center whenever needed. Those who fail to recover before or at discharge will undergo investigations following national guideline procedures to understand the reasons for failure and will be managed accordingly.

Table 2 Schedule of intervention and assessments

Visits (week)		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**20**	**24**
Supplementation		**YES**													**NO**		
Enrollment & socio-demographic data		×															
Anthropometry & morbidity	MAM	×		×		×		×		×		×		×	×	×	×
	SAM	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Dietary intake assessment		×						×									×
Adherence			×	×	×	×	×	×	×	×	×	×	×	×			
Serious adverse events			×	×	×	×	×	×	×	×	×	×	×	×			

Mothers will be encouraged to return to the health center any time the child presents a nutritional or health-related concern. They will be received by health center personnel, and a clinical examination will be conducted to ascertain any problems. A report summarizing the conclusions of the spontaneous visit will be given to the study staff during the next scheduled visit at the health center.

Data collection procedures

Anthropometry

At each visit, weight, height, and mid-upper arm circumference will be assessed. Recumbent length or height will be measured to the nearest 1 mm using a SECA 207 scale. Body weight will be measured by use of Uniscale electronic scales up to a precision of 100 g (SECA, Germany); weighing scales will be calibrated on a weekly basis. The MUAC will be measured to the nearest 1 mm using a MUAC measuring tape. All measurements will be performed in duplicate. Standardization sessions will be conducted with data collectors every six [6] months to assess their performance (accuracy and precision) in measuring anthropometric parameters.

Morbidity assessment

Morbidity will be assessed by interviewing caregivers with validated questionnaires. The monitoring will be performed in all study groups. Data on infectious episodes (type and duration) and possible side effects suffered by the child during the two weeks prior to the visit will be recorded.

Adherence

To measure adherence, mothers will be asked to bring back the empty sachets of food supplements consumed between 2 visits and unused sachets. Questions will also be asked to the mothers on the difficulties encountered when feeding the food supplements to their children and the adverse effects observed following the consumption of the food supplements.

Serious adverse events

While we expect no serious adverse events (SAEs) in using food supplements, mothers/caregivers will be instructed to report any adverse events occurring during the trial that can be related to the interventions. The reported SAEs will be further investigated by the study investigators and recorded for all participants throughout the duration of the study. All SAEs will be followed according to current treatment guidelines until resolution or until a stable clinical endpoint is reached.

Data management and analysis

Data collection will be done in health centers and in the community by staff trained and recruited for this purpose in collaboration with health center staff from the Ministry of Health. All the data will be collected on paper and saved on computers (or tablets) using a controlled input mask. Standard operating procedures (SOPs) will be developed, and the processes and data entry forms and their procedures and instructions will be described. The data entry mask will be uploaded onto computers (and tablets) using the REDCap application (https://projectredcap.org/). The data will be sent to an online encrypted server as regularly as possible to allow quality control of the data throughout the study. At the end of the study, the database will be downloaded from the server before the data are cleaned and then analyzed anonymously. Only the study investigators will be allowed to access the study data via a secure internet connection.

The data will be transferred to STATA and analyzed following a statistical analysis plan. The outcomes will be measured at two timepoints, and the analysis will be by intention-to-treat, according to prespecified 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 that differ at baseline between study groups. These factors were previously reported to be associated with recovery. This adjustment strategy will account for baseline imbalances and will increase the statistical power by reducing variance. All analyses will be adjusted for health center (fixed effect) to reflect the stratified sampling design. Unless specified otherwise, continuous outcomes measured at one time point will be analyzed using ordinary least squares regression with the same adjustment variables.

Monitoring

An independent Data and Safety Monitoring Board will be used for this study. Enrollment numbers, lost to follow-up, serious adverse events, and withdrawals will be monitored by the study coordinator. All SAEs will be investigated and recorded on a case-by-case basis. A continuing review will also be completed periodically. Any deviations will be reported to the Ethics Committee and the study sponsor. At all times, the Ethics Committee will be promptly provided with information from the principal investigator as needed.

Ancillary care

The fees for ancillary care are covered by the current National Free Healthcare Program in Burkina.

Participants suffering harm due to their participation in the trial will be covered by the project.

Confidentiality

The privacy, anonymity and confidentiality of all data/information identifying the participants will be strictly maintained. During the trial, the data files containing personal identifying information will be stored on a server. Only the principal investigators and the project coordinators will be able to access those files. Participants and/or caregivers will be able to freely communicate with the local Principal Investigators of the study (contact information will be provided on the consent form).

Dissemination plan

We plan to disseminate and share the findings from this study, both locally with participants and their communities, the Ministry of Health and through presentations at conferences for nutritionists and relevant professionals and international institutions.

Papers on the study results will be published in peer-reviewed journals. All investigators contributing to the implementation of the studies and publication of results will be included as authors.

Discussion

Different strategies and food products are used in the management of acute malnutrition. In this paper, the protocol of an individually randomized and stratified controlled trial is described in which 6- to 23-month-old children with moderate and severe uncomplicated acute malnutrition receive a food supplement targeting the gut microbiota in the intervention groups and standard therapeutic or supplementary food in the control groups. This study will test the efficacy of a food that targets the gut microbiota to promote sustained recovery from acute malnutrition. The results of this study will contribute to a growing body of evidence on a knowledge gap that is central to the management of acute malnutrition and the prevention of its complications.

The key features of the present trial include the first formative study for a better understanding of the acceptability of the novel food. This study will provide evidence on the effectiveness of microbiome-directed food for treating both moderate and severe acute malnutrition and preventing relapses. The results will further strengthen and refine the WHO's recommendation on the use of alternative food products in the management of uncomplicated acute malnutrition.

Abbreviations

CHW	Community health worker
CMAM	community-based management of acute malnutrition
CSB	Corn soy blend
CSPS	Centre de santé et de promotion sociale
GM	Gut microbiota
HAZ	height-for-age z-score
ICDDR, B	International Centre for Diarrhoeal Disease Research, Bangladesh
MAM	Moderate acute malnutrition
MDCF	Microbiome-directed complementary food
MoH	Ministry of Health
MUAC	Mid-upper arm circumference
POC	Proof-of-concept
RUSF	Ready-to-use supplementary food
RUTF	Ready-to-use therapeutic food
SAE	Serious adverse event
SAM	Severe acute malnutrition
SDG	Sustainable development goal
SFP	Supplementary food program
SOP	Standard operating procedure
UNICEF	United Nations Children´s Fund
WAZ	Weight-for-age z-score
WFP	World food program
WHA	World health Assembly
WHO	World health organization
WHZ	Weight-for-height z-score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40795-025-01045-x.

Supplementary Material 1

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Not applicable.

Author contributions

H.B.L. wrote the manuscript; H.B.L., S.K., S.J. and A.K., designed the study and the protocol; H.B.L., J.S., A.K. and S.K. designed the study material tools; all authors contributed substantially to the manuscript and approved the final version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study protocol was approved by the MoH Health research ethics Committee (MOH; CERS 2022-03-044; approval date: 2 Mars 2022) and by the technical committee of clinical trials examination. The protocol is registered at Clinicaltrials.gov Protocol registration and results system (NCT05586139; https://register.clinicaltrials.gov/; registration date: 22 September 2022). Amendments to the study protocol will be submitted to the Ethics Committee, and the trial registry will be updated accordingly. This study will be conducted according to the principles of the Declaration of Helsinki. Before the participants' enrollment, an explanation will be provided regarding the informed consent contents, study procedures, objectives, and potential outcomes and their participation are voluntary. All participants should provide an informed written consent form. All data will be handled with strict confidentiality, assuring the anonymity throughout the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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