Efficacy of alternative RUTFs for treatment of child wasting and prevention of relapse

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List of abbreviations

ABC	Activity-Based Costing
CMAM	Community Management of Acute Malnutrition
CoC	Continuum of Care
CSPS	Centre de Santé et Promotion Sociale
DALY	Disability-adjusted life year
DSMC	Data Safety and Monitoring Committee
ELISA	Enzyme-linked immunosorbent assay
HAZ	Height-for-age z-score
IFPRI	International Food Policy Research Institute
IRB	Institutional Review Board
IRSS	Institut de Recherche en Sciences de la Santé
LAZ	Length-for-Age Z-score
MAM	Moderate Acute Malnutrition
NGO	Non-governmental organization
OTP	Outpatient Treatment Program
PP	Per-protocol
pp	Percentage point
RUSF	Ready-to-Use Supplementary Food
RUTF	Ready-to-Use Therapeutic Food
SAM	Severe Acute Malnutrition
SAP	Statistical analysis plan
SD	Standard deviation
SMS-RUTF	Soy-maize-sorghum-based RUTF
SOP	Standard operating procedure
S-RUTF	Soy-based RUTF
TMF	Trial Master File
UN	United Nations
UNICEF	United Nations International Children's Emergency Fund
WAZ	Weight-for-Age Z-score
WHO	World Health Organization
WHZ	Weight-for-Height Z-sore
WLZ	Weight-for-Length Z-score

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Abstract

Background

Acute malnutrition is the most life-threatening form of undernutrition. Moderate and severe acute malnutrition (MAM, SAM) are effectively treated with ready-to-use therapeutic foods (RUTFs) but there is a need to lower the cost of treatment and improve treatment regimens to reduce risk of relapse MAM/SAM episodes following recovery. The currently used standard formulation of RUTF contains peanuts and dairy, which pose problems due to their high cost, the need to import ingredients to the Global South (in the case of dairy), and risk of aflatoxin (in the case of peanuts). Before alternative formulations of RUTF can be recommended, however, there is the need for data on the efficacy of these formulations on recovery rates and to what extent recovery is sustainable. Sustainable recovery implies a lower rate of post-treatment relapse.

Objectives

Our objectives are as follows: (1) To assess the non-inferiority of novel soy-maize-sorghum (SMS-) RUTF and soy-based (S-) RUTF on treatment recovery to standard RUTF; (2) To assess the superiority of SMS-RUTF and S- RUTF on post-recovery relapse compared to standard RUTF; (3) To assess the costs of a treatment course of SMS-RUTF, S-RUTF, and standard RUTF; (4) To assess the effect of SMS-RUTF and S-RUTF on microbiome composition and intestinal inflammation

Methodology

We will conduct a facility-based, individually randomized controlled trial with three arms allocated in a 1:1:1 allocation ratio in 30 health facilities (Centre de Santé et Promotion Sociale [CSPS]) in Burkina Faso. We will randomize 1080 children with MAM and 1080 children with uncomplicated SAM 6-59 months of age to receive treatment with one of the following RUTFs: (1) standard of care, milk- and peanut-based RUTF (control group); (2) SMS-RUTF free of milk and peanuts and high in fiber (intervention 1); or (3) S-RUTF free of milk and peanuts (intervention 2). Children will be enrolled upon presentation to facilities for MAM or uncomplicated SAM treatment. Follow up visits will be weekly during treatment for SAM children and bi-weekly during treatment for MAM children, and monthly for 3 months following discharge from treatment. The primary study outcomes are anthropometric recovery at discharge (a non-inferiority analysis) and relapse to MAM or SAM within the 3 months following recovery (a superiority analysis). We will employ an activity-based micro-costing approach to collect cost data on the direct and indirect medical costs, opportunity costs to caregivers, personnel, and overheads associated with outpatient MAM or SAM treatment. Fecal samples will be collected from children at a subset of facilities (5 facilities, ~60 children per treatment arm), at enrollment (initiation of treatment), discharge from treatment, and 3-months post-discharge. Enrollment is planned to begin in October 2024, and follow up is planned to be completed in August 2025. Final results are planned to be available in December 2025.

Introduction

Globally, 45 million children under the age of five suffer from wasting, a form of acute malnutrition characterized by extreme loss of muscle and fat tissue (1). Acute malnutrition dramatically increases the risk of death; compared to well-nourished children, children with moderate acute malnutrition (MAM) are 3.4 times more likely to die, and this probability increases to a staggering 11.6 times in children with severe acute malnutrition (SAM) (2). Child acute malnutrition is the underlying cause for an estimated annual 875,000 deaths of children under 5 years of age, representing about 12.6% of all deaths in this age group worldwide (3).

More than a decade ago, the World Health Organization (WHO) endorsed the community-based management of acute malnutrition (CMAM) model to address severe acute malnutrition. The specific aim was to tackle the low coverage and high case-fatality of the existing inpatient treatment model (4). CMAM entails the active case-finding and referral of children with severe acute malnutrition by community health workers or volunteers to first-line health services and the outpatient treatment of children with severe acute malnutrition who demonstrate sufficient appetite and have no medical complications (5). A key development that facilitated the shift to the outpatient model was the introduction of energy-dense ready-to-use therapeutic foods (RUTF). RUTF provides a convenient and safe way to deliver the energy and nutrients needed for children suffering from severe acute malnutrition to recover. The supplements can be consumed directly from the package, do not require cold-chain, and are microbiologically safe (6).

Current World Health Organization guidelines stipulate that at least half of the proteins in the RUTF should come from milk products (5,7). The milk content, however, constitutes 25% of the total product cost and makes RUTF very expensive for use in resource-constrained settings. In addition, it reduces the products environmental sustainability and increases the need to import ingredients into these settings (8). New RUTF formulations that replace the milk protein (the most expensive ingredient) with cheaper sources of quality protein such as soy, maize, and sorghum have been developed. UNICEF has also noted the importance of developing non-peanut based RUTFs in regions where peanuts (which constitute 15% of total product costs) are not a staple food to improve local acceptance as well as to further reduce cost (7,9). Additionally, removing peanut ingredients would eliminate the risk of aflatoxin exposure. Replacing milk and peanut protein by other, plant-based proteins in RUTF reduces product cost, reduces the supplement's carbon footprint, and, when the alternative ingredients are locally available, may increase adoption by local governments and acceptance by local communities. Reducing the cost of RUTF can thus contribute significantly to improving the affordability of and access to the treatment for SAM, thus increasing treatment coverage.

Before scaling-up the use of new and more affordable RUTF formulations, rigorous evidence on their efficacy and cost-efficacy is needed. The proposed project seeks to generate this evidence for two alternative RUTF formulations that are free of milk and peanut. Furthermore, one of the formulations has a significantly higher fiber content compared to the currently used milk-based RUTF (5.0g vs. 0.75g per 100g). A recent pilot study in Bangladesh found that a milk-free and fiber-rich ready-to-use formula had superior outcomes in weight gain and recovery from acute malnutrition associated with a change in microbiota components linked to child growth (16). The study also reported significantly lower relapse rates than the standard formulation. However, a Cochrane review of RUTF treatment reported relapse rates were higher in children receiving an alternative RUTF (many of which contained lower milk powder

than the comparator, or no milk powder) (10). Additional studies are warranted to confirm the prebiotic effect of fiber-rich formulas on weight gain and gut health, and the prevention of post-treatment relapse.

This study will test the efficacy of peanut-free and milk-free RUTF formulations for the treatment of acute malnutrition in young children. The study responds to a UNICEF call for more research that supports inclusion of novel plant-based RUTF products in their portfolio and create more opportunities for local production of RUTF. As a consequence, the results will have an immediate impact on UNICEF's and countries' RUTF strategy and are expected to contribute to reducing the cost of treating children with acute malnutrition.

Research objectives

Our primary research objectives are as follows:

1. To assess the non-inferiority of novel Soy-Maize-Sorghum (SMS-) RUTF and Soy-based (S-) RUTF on treatment recovery to standard RUTF
2. To assess the superiority of SMS-RUTF and S- RUTF on post-recovery relapse compared to standard RUTF

Our secondary research objectives are as follows:

1. To assess the costs of a treatment course of SMS-RUTF, S-RUTF, and standard RUTF
2. To assess the effect of SMS-RUTF and S-RUTF on intestinal permeability/inflammation and microbiome composition including enteropathogen burden
3. To assess the acceptability of SMS-RUTF and S-RUTF
4. To assess the non-inferiority of SMS-RUTF and S-RUTF on length of stay in treatment among recovered children
5. To assess the non-inferiority of SMS-RUTF and S-RUTF on weight gain during treatment
6. To assess the non-inferiority of SMS-RUTF and S-RUTF on default from treatment
7. To assess the non-inferiority of SMS-RUTF and S-RUTF on transfers to inpatient treatment
8. To assess the non-inferiority of SMS-RUTF and S-RUTF on non-response to treatment
9. To assess the non-inferiority of SMS-RUTF and S-RUTF on adherence to treatment services
10. To assess the non-inferiority of SMS-RUTF and S-RUTF on compliance to treatment services
11. To assess the non-inferiority of SMS-RUTF and S-RUTF on anthropometry at discharge from treatment
12. To assess the superiority of SMS-RUTF and S-RUTF on anthropometry at 3-months post-discharge
13. To assess the superiority of SMS-RUTF and S-RUTF on relapse to SAM post-discharge among recovered children
14. To assess the superiority of SMS-RUTF and S-RUTF on relapse to MAM post-discharge among recovered children
15. To assess the non-inferiority of SMS-RUTF and S-RUTF on hemoglobin at discharge and superiority of SMS-RUTF and S-RUTF on hemoglobin at 3-months post-discharge
16. To assess the non-inferiority of SMS-RUTF and S-RUTF on anemia at discharge and superiority of SMS-RUTF and S-RUTF on anemia at 3-months post-discharge

Methodology

Study setting and site selection

Burkina Faso is a land-locked country in West Africa with a high burden of wasting, with national prevalences estimated at 9.7% of children under age 5 (11). Burkina Faso has seen deteriorating humanitarian conditions since 2020, with numbers of internally displaced persons (IDPs) exceeding 2 million due to security incidences, and increasing populations refugees primarily from Mali. In addition to the intensifying displacement, the food security situation has deteriorated significantly and 630,000 children in Burkina Faso are projected to be acutely malnourished in 2023. This study will be conducted in 30 health centers (Centres de Santé et Promotion Sociale [CSPSs]) in the Hauts-Basin region of Burkina Faso. CSPSs with the highest caseloads in the Dande, Dafra, Karangasso, and Hounde health districts will be selected.

Study design

This will be a facility-based, individually randomized, controlled trial with three arms, including two interventions (SMS-RUTF and S-RUTF) and one control arm (standard RUTF), and a 1:1:1 allocation ratio. Children will be enrolled upon initiation of MAM or SAM treatment and followed for 3 months post-discharge from treatment. The national CMAM protocol of Burkina Faso will be followed when evaluating the different RUTFs.

Randomization procedure

A statistician who is not part of the research team will generate a randomization scheme for the allocation of the 3 supplements. Each unique randomization number is randomly allocated to 1 of 9 letter codes (e.g., A, E, I, Z, K, T, N, E, S)—3 letters for the SMS-RUTF supplement, 3 letters for the S-RUTF supplement and 3 letters for the standard RUTF (control group)—using a computer program in permuted blocks of 15. Without notifying the investigators, the statistician will inform the producers which letters to print on the package of each supplement. Information regarding the assignment of the letter codes to the intervention and control supplements is sealed in opaque envelopes, who locked the envelope away until analysis was completed. Before the study started, the clinical research coordinator will seal each of the randomization numbers with the corresponding letter codes of the RUTF supplements into separate opaque envelopes that were marked with unique participant numbers to be attributed at study inclusion. At study inclusion, the study nurse opens the next sealed envelope in the presence of an eligible mother-child pair (in order of arrival) and provides them with the RUTF supplement according to the letter code. The participant's number, as well as the letter code, will be written down on the study participant's card.

Study participants and determination of eligibility

The population for this study will be children 6-59 months old with MAM or uncomplicated SAM presenting to the study facilities. MAM will be defined as middle upper arm circumference (MUAC) ≥ 11.5 and < 12.5 cm, or weight-for-length/height z-score (WLZ/WHZ) ≥-3 and < -2. Uncomplicated SAM (i.e., cases of SAM that are eligible for outpatient treatment) will be defined by all the following criteria: (i) MUAC < 11.5 cm or WLZ/WHZ < -3, (ii) no clinical complications, and (iii) child passes the appetite test (the child eats at least the amount of RUTF required for passing the appetite test as per Burkina Faso national guidelines (12)).

The inclusion criteria are therefore:

- Age 6-59 months
- MUAC < 12.5 cm, or WLZ/WHZ < -2
- Absence of clinical complications
- Pass the appetite test
- Accompanied by caregiver or legal guardian
- Caregiver or legal guardian consents to participate

Children will be excluded if they meet any of the following criteria:

- Acute malnutrition requiring hospitalization (presence of clinical complications, failure to pass the appetite test, or presence of bilateral pitting edema (12))
- Known allergy to any of the ingredients in the RUTF products
- Already enrolled in MAM or SAM treatment program
- Presence of physical abnormalities that make measurement of anthropometry impossible
- Caregiver has intention to move out of the study area within the next 6 months
- Children referred from in-patient facilities to continue in ambulatory care

Children will be screened for eligibility upon presentation at the study health centers, and will be determined to be eligible upon diagnosis with MAM or uncomplicated SAM. Because treatment coverage is low in Burkina Faso, the project will organize mass screening campaigns in surrounding villages to detect and refer all MAM and SAM cases for treatment. Additionally, the project will strengthen wasting screening at consultations and well-baby vaccination visits at the study health centers to increase coverage of screening and referrals to treatment.

Informed consent

The caregivers or legal guardian of eligible children will undergo the informed consent process. The Information Sheet and Informed Consent form will be read to the caregiver/ legal guardian of the eligible child in their language. The caregiver/ legal guardian will be given opportunities to ask any questions, and his/her comprehension of the form will be confirmed. He/she will sign the consent form if he/she agrees to participate. If the caregiver/ legal guardian is illiterate, a thumbprint will be collected to substitute for a signature.

Study intervention and control arms

Children admitted into MAM or SAM treatment at the study centers will be randomized to one of three RUTF formulations:

- **Standard of care RUTF (control)**: composed of milk powder, sugar, vegetable oil, peanut butter, vitamins, and minerals and low in fiber (0.75g per 100g)
- **Alternative, soy-maize-sorghum-RUTF (SMS-RUTF) formulation (intervention 1)**: a milk- and peanut-free product with added crystalline amino acids that provide significantly more fiber (5.0g per 100g)

- **Alternative, soy-based RUTF (S-RUTF) formulation (intervention 2):** a milk- and peanut-free product with added crystalline amino acids

Burkina Faso national guidelines for MAM and SAM treatment will be followed for dosing the products and all other aspects of treatment (Table 1 and

Table *2*). Thus, all children will receive the standard of care for CMAM treatment in Burkina Faso, with the only difference between treatment arms being the product received. Burkina Faso national guidelines for CMAM are detailed in the guideline document (12). Briefly, upon admission to treatment for SAM, children will undergo medical evaluation and receive routine antibiotics and rapid diagnostic test for malaria as well as other treatment as indicated in the guidelines. The caregiver of the child will be provided with RUTF and instructed on how to use to use it. Children will be followed weekly at the health center to be re-evaluated. At the follow-up visits, children's anthropometry will be measured, a clinical examination will be performed, and the caregiver will be provided with another 7-days' supply of RUTF with instructions. Children will be treated a maximum of 12 weeks and will be eligible to be discharged when they have achieved anthropometric recovery (defined in Table 3). For MAM, upon admission to treatment, children will be provided with RUTF to be used as a food supplement in addition to the child's usual diet. Caregivers will be provided with the product and instructed on its use, and receive nutritional counseling as per guidelines. Children will receive medical treatments as indicated in the guidelines, and instructed to return to the health facility every two weeks for monitoring. Children will be treated for a maximum of 12 weeks and be eligible for discharge when they have achieved anthropometric recovery.

Table 1. Burkina Faso guidelines for dosage for MAM (12)

Sachets per day (92 gram sachets)	Sachets per week (92 gram sachets)	Sachets per two weeks (92 gram sachets)
1	7	14

Table 2. Burkina Faso guidelines for dosage for SAM (12)

Child's weight (kilograms)	RUTF - grams		RUTF – sachets (92 grams)	
	Grams per day	Grames per week	Sachets per day	Sachets per week
3.0-3.4	105	750	1 ¼	8
3.5 – 4.9	130	900	1 ½	10
5.0 – 6.9	200	1400	2	15
7.0 – 9.9	260	1800	3	20
10.0 – 14.9	400	2800	4	30
15.0 – 19.9	450	3200	5	35
20.0 – 29.9*	500	3500	6	40

Storage of product

All products will be stored according to instructions from the manufacturer, in a dry and cool place at a temperature below 30° C out of direct sunlight. Prior to providing participants with products, the products will be inspected visually for damage. Quality control procedures will be detailed in a study standard operating procedure (SOP).

Outcomes

The outcomes of the study, their definitions, and type of analysis (non-inferiority or superiority) are listed in Table 3. Treatment outcomes will be evaluated through non-inferiority, and post-treatment outcomes will be evaluated through superiority analyses. This is because the intervention products may have the important benefits described above of being lower cost than the standard RUTF, increased potential to be produced locally, and free of aflatoxin, but evidence is needed to confirm they are acceptably similar in treatment outcomes. The composition of these alternative formulations may also improve gut health, possibly reducing the risk of relapse. Thus, post-discharge relapse outcomes are analyzed in superiority analyses.

Table 3. Primary and secondary study outcomes

Outcomes	Definition	Type of analysis
Primary outcomes		
Anthropometric recovery at discharge	WLZ ≥ -2 and MUAC ≥ 125 mm and absence of bilateral pitting edema for two consecutive visits	Non-inferiority
Relapse to wasting within 3-months post-discharge	A new episode of wasting (defined as WLZ/WHZ < -2 or MUAC < 125 mm or presence of bilateral pitting edema) within the 3-month period following recovery from the index wasting episode, among children who recovered from their index episode	Superiority
Secondary outcomes		
Length of stay (LOS) among recovered children:	The number of days between the day the child is admitted to treatment and the day the child is determined to be recovered and thus discharged from treatment	Non-inferiority
Weight gain	Change in child's weight (gram/kilogram/day) between weight on day of admission to treatment and day of discharge	Non-inferiority
Default from treatment	Child is absent for two consecutive visits, declared a defaulter on the second visit	Non-inferiority
Transfer to inpatient treatment	Referral or admission to hospital for inpatient treatment during the treatment course	Non-inferiority
Non-response to treatment	Any of the following criteria are met: Absence of weight gain after 5 weeks or at the third visit; weight loss for more than 4 weeks in the program or at the second visit; loss of more than 5% of body weight compared to admission weight at any time; or anthropometric recovery criteria not met after 3 months of follow-up in CMAM	Non-inferiority

Adherence to treatment services	Caregiver attends the recommended schedule of visits and receive RUTF supply	Non-inferiority
Compliance to treatment services	The child receives the recommended dose of the RUTF each day	Non-inferiority
Anthropometry at discharge from treatment	WLZ/WHZ, MUAC, weight, height/length, LAZ/HAZ and WAZ at discharge from treatment	Non-inferiority
Anthropometry at 3-months post-discharge	WLZ/WHZ, MUAC, weight, height/length, LAZ/HAZ and WAZ at 3-months post-discharge	Superiority
Relapse to SAM	A new episode of SAM (WLZ/WHZ < -3 or MUAC < 115 mm or presence of bilateral pitting edema) within the 3-month period following recovery from the index wasting episode	Superiority
Relapse to MAM	A new episode of MAM (WLZ/WHZ <-2 and ≥-3, or MUAC <125 mm and ≥115 mm) within the 3-month period following recovery from the index wasting episode	Superiority
Morbidity	Indication of morbidity (acute respiratory infections, diarrhea, fever, or malaria) on health center card	Non-inferiority
Hemoglobin at discharge	Hemoglobin concentration (grams/liter) at discharge	Non-inferiority
Hemoglobin at 3-months post-discharge	Hemoglobin concentration (grams/liter) at 3-months post-discharge	Superiority
Anemia at discharge	For children 6-23 months of age: Hemoglobin concentration < 105 gram/liter at discharge For children 24-59 months of age: Hemoglobin concentration < 110 gram/liter at discharge	Non-inferiority
Anemia at 3-months post-discharge	For children 6-23 months of age: Hemoglobin concentration < 105 gram/liter at discharge For children 24-59 months of age: Hemoglobin concentration < 110 gram/liter at discharge	Superiority

Sample size

We estimate a total sample size of 1080 children with SAM (360 per arm) and 1080 children with MAM (360 per arm) will provide at least 90% statistical power to demonstrate non-inferiority for each comparison, with a non-inferiority margin of 10 percentage points, assuming a recovery rate in the control of 77% (Table 4). For relapse outcomes, sample size will be smaller, and thus power will be lower, because only recovered children will be included in the analysis. All calculations assume a one-sided $\alpha = 0.05$ for non-inferiority and two-sided $\alpha = 0.05$ for superiority analyses.

Table 4. Sample size calculations

*Scenarios with at least 80% power are **bolded**.*

Primary outcome	Analysis type	Sample size per arm	Outcome prevalences reported in literature	Non-inferiority margin or detectable effect size	Assumption on control group outcome prevalence/means in sample size calculations	Power per comparison
Anthropometric recovery at discharge	Non-inferiority	360 MAM and 360 SAM children/arm enrolled; 306 MAM and 306 SAM children in analysis after 15% attrition	MAM recovery (with RUSF*): 73% (13); 73% (14); 85% (15) SAM recovery: 55.4% (16); 82.3% (17); 76% (18); 71% (pooled estimate from meta-analysis) (19)	10 percentage points (absolute difference)	**55.4% (vs 45.4%)**	**85.6%**
					77.0% (vs 67.0%)	**90.0%**
					82.3% (vs 72.3%)	**96.8%**
Relapse to wasting within 3-months post-discharge	Superiority	236 children/arm in analysis (assuming 77% of the 306 children recover)	Post-MAM relapse: 30% within 3 months (period prevalence) (20); 33% within 12-months (21) Post-SAM relapse: 6.8% 3-month cumulative incidence (22); 24% 2-month cumulative incidence (23); 30% within 3-months (unpublished); 2.6 episodes per child-year (unpublished); 1.3	35% relative reduction (incidence rate ratio = 0.65)	**Incidence of 2.6 episodes per child-year**	**80.0%**
					Prevalence of 30% (vs 20%)	71.0%

			episodes per child-year (unpublished)			

*RUSF = ready-to-use supplementary food

Study procedures

All staff will be trained in the study procedures, in order to screen for eligibility, determine eligibility, collect informed consent, administer study products, and conduct follow up procedures in accordance with the trial protocol and SOPs. Before enrollment of the first participant, all study procedures will be piloted for 2 weeks at the study sites to check for any procedural problems, collect feedback from facility staff and communities, and implement any revisions to procedures as needed.

After informed consent is obtained, a unique participant number will be assigned to the participant. Clinical information related to the child's wasting episode, including documentation of routine medications received, child's anthropometry, and clinical status. In addition, the child's medical history and clinical presentation details will be abstracted from their medical records as documented by the study clinician, and copies of the medical records will be stored in the child's study file.

The study nurse will provide counseling on the specifics of wasting treatment as per Burkina Faso guidelines, including the schedule of visits, how to use the RUTF throughout the treatment course, and the duration of treatment. As per Burkina Faso guidelines, the caregiver will return regularly to the facility for follow-up care for their child (weekly for SAM; bi-weekly for MAM), during which they will receive clinical exam to assess morbidity, measurement of anthropometry, and receive another 7-day supply of RUTF. The nurse will answer any questions the caregivers might have. Adherence will be assessed at these follow up visits through caregiver report.

When the child meets the criteria for discharge, children will be counseled to return to the facility for post-discharge follow up monthly for 3 months. At these post-discharge follow-up visits, caregivers will be asked about any admissions to hospital for wasting in the previous month, and the child will be screened for wasting. More details on data collection are given in the following section and in Table 7.

Anthropometric and clinical procedures

Anthropometric measurements will be taken at treatment initiation and discharge, weekly during the treatment course for SAM children and bi-weekly for MAM children, and monthly during the post-discharge follow-up. The child's weight will be taken using an electronic scale to the nearest 100g. The length will be measured with a measuring board to the nearest 1 mm. MUAC will be measured using a non-stretch tape with 0.1 cm accuracy. All measurements will be taken twice by the study nurses and the average calculated. Weight-for-age, weight-for-length/height, and length/height-for-age z-scores will be calculated using the WHO 2006 growth standards (24).

All children will be tested for malaria upon admission as per national guidelines for wasting treatment (12) through rapid diagnostic test using capillary blood. Capillary blood will be collected from all children via finger prick to measure hemoglobin concentration, at baseline (initiation of treatment) and at discharge.

Costing

We will employ an activity-based costing-ingredients (ABC-I) approach to collect and analyze data on costs incurred in each treatment arm. A societal perspective will be used, which includes all financial and

economic costs regardless of who incurs them; i.e. health system, implementing partners, and patients (25,26). This will include costs and opportunity costs to caregivers. We will have two activities, which are the treatment of MAM and the outpatient treatment of SAM. For these activities, we will assess the cost categories listed in Table *5*.

Table 5. Cost categories and their descriptions for costing analyses

Cost category	Description
Direct medical costs	Costs of all equipment, procedures, and consumables (medications and nutrition commodities [RUTFs]) used in the outpatient treatment of SAM or MAM, beginning at admission and ending at discharge
Indirect medical costs	Costs to caregivers incurred due to receiving outpatient SAM treatment, including cost of transportation and any food or lodging costs
Opportunity costs to caregivers	The valuation of the time that caregivers spend on having their child treated for wasting, including time traveling to and spent at OTPs. Missed income will be calculated, and, for caregivers who do not have paid employment outside the home, opportunity costs will be calculated using 60% of national GDP (27,28) and estimated amount of time spent participating in the program.
Personnel	Salaries of health workers involved in the admission, follow up, and discharge of outpatient SAM children
Overheads	Costs of infrastructure, management, administration, and logistical support

Data sources will include accounting records and interviews. We will collect accounting data from the study hospitals that cover the time period of interest, which will provide an exhaustive list of inputs and materials and support used in the program. We will conduct interviews with staff members and other key actors involved in the treatment of SAM, and the management and logistical support. A subset of caregivers will be interviewed about their direct, indirect, and opportunity costs for the admission visit as part of the baseline questionnaires, and will be asked about these costs for the follow-up visits and discharge visit at the discharge visit.

Costing data from accounting records and interviews will be entered into Excel spreadsheets, which will be used for the analysis. Data be securely stored on password-protected computers and on secure servers.

We will estimate total costs, and the cost-efficiency and cost-effectiveness of the intervention. Cost-efficiency refers to the estimates of cost per programmatic output, allowing for the comparison of programs that produce the same output. Cost-effectiveness refers to cost per health outcome, allowing an assessment of value-for-money of a health intervention given its health impacts. All outcomes are defined in Table 6.

If the interventions are demonstrated to be superior for relapse, we will calculate the cost per DALY averted between each intervention arm and the control. To do this, we will construct a decision tree model to compare the costs and effects of treatment with the intervention RUTFs relative to standard RUTF. The health states that will contribute to DALYs are SAM and death. The effects of the intervention package will include effects on relapse. Disability weights will be sourced from the most recently published Global Burden of Disease disability weight estimates. We will not employ age-weighting and discounting (29). Both probability and deterministic sensitivity analyses will be conducted. If the interventions are demonstrated to be non-inferior for both recovery and relapse outcomes, we will calculate the difference in costs between each intervention arm and the control.

All analyses will be conducted using TreeAge, Excel, and Stata software.

Table 6. Costing outcomes and their definitions

Outcome	Category	Definition
Cost per MAM child admitted into treatment	Cost-efficiency	Total cost of MAM treatment divided by the number of MAM children admitted into treatment during that time period
Cost per SAM child admitted into treatment	Cost-efficiency	Total cost of SAM treatment divided by the number of SAM children admitted into treatment during that time period
Cost per treated MAM child recovered	Cost-effectiveness	Total cost of MAM treatment divided by the number of MAM children recovered during that period (the number admitted into treatment during that time period multiplied by recovery rates)
Cost per treated SAM child recovered	Cost-effectiveness	Total cost of SAM treatment divided by the number of SAM children recovered during that period (the number admitted into treatment during that time period multiplied by recovery rates)
Cost per DALY averted	Cost-effectiveness	Difference in the cost of treatment between intervention and control groups divided by difference in DALYs between intervention and control groups

Acceptability sub-study

We will conduct a rapid assessment of acceptability of each product in a convenience sample of 40 SAM and MAM children, after the study enrollment target has been reached. A total of two feeding sessions will be organized with a washout period of two hours in between sessions. The sample of caretaker-child dyads will be divided in strata by child age and subsequently randomly be allocated to one of 4 schedules

per age stratum: i) AB; ii) BA; iii) AC; iv) CA with A being the standard RUTF, B the SMS-RUTF and C the S-RUTF. For each session, a single dose of 92 g of RUTF will be provided. Caretakers will be asked to feed their child ad libitum for 30 min. The feeding will be directly observed by data collectors. The remaining portion will be weighed, and the consumed quantity will be calculated by subtraction. Data collectors will observe the feeding experiment and collect qualitative data on caretakers' and children's behavior during the feeding experiment. A short post-exit interview with caretakers will collect the caretakers' perceptions of the different RUTF products.

Fecal sample analysis sub-study

Children with SAM suffer from higher levels of gut inflammation, more immature gut microbiome profiles, and higher enteric pathogen burdens than their well-nourished counterparts (30–32). While standard RUTF is effective in aiding anthropometric recovery, this compromised gut health may not be addressed by standard formulations, as children with SAM can experience persistent microbiome maturity even after therapeutic feeding (33). Alternative formulas may hold promise for improving gut health, through pathways such as high fiber and/or short chain fatty acids content (31,34). A pilot study in Bangladesh reported a milk-free and fiber-rich ready-to-use food had superior outcomes in anthropometric outcomes among children with wasting, associated with a change in microbiota components linked to child growth (16). Thus we hypothesize that these new formulations may impact post-recovery outcomes by improving gut health. The objective of this sub-study is thus to assess if the alternative RUTFs have any impact on two specific sets of mechanistic outcomes (intestinal permeability/inflammation and microbiome profile including enteropathogen burden) that can support this theory of change of the intervention on the main study outcomes.

A first hypothesis by which milk- and peanut-free RUTF can lead to higher rates of sustainable recovery is reducing intestinal permeability and inflammation as compared to standard RUTF. For this purpose, we propose to analyze three indicator molecules. α-1 antitrypsin is a marker for intestinal protein loss and can serve as an indicator for gastrointestinal disorders that affect gut integrity and intestinal permeability. Fecal neopterin and myeloperoxidase are markers for intestinal inflammation often associated with the presence of enteropathogens. All three molecules are analyzed using commercially available enzyme-linked immunosorbent assays (ELISAs). A second hypothesis is that alternative RUTFs provide fewer substrates for enteropathogen growth and lead to improved gut microbiota abundance and age-appropriate diversity. For this purpose, we will assess a set of common enteropathogens using a TaqMan Array Card[1] assay specifically designed for pathogens associated with child growth. Fecal microbiota will

[1] Enteropathogen detection will be conducted using the TaqMan Array Card (TAC) system, a 384-well singleplex real-time PCR format used to detect 62 infection targets 62 including viruses, bacteria, protozoa and helminths, specifically: *A. duodenale & lumbricoides*; *B. fragilis & hominis*; *C. belli, cayetanensis, coli, concisus, difficile, hominis, jejuni, parvum, troglodytis, & upsaliensis; E. bieneusi & histoly tica*; *G. lamblia*; *H. pylori*; *M. tuberculosis*; *N. americanus*; *P. shigelloides*; *S. enterica, flexneri, mansoni, sonnei, & stercoralis*; *T. solium & trichiura*; *V. cholerae*; enteroaggregative *E. coli* [EAEC (aaiC, aatA, & aagR)], enteroinvasive *E. coli* [EIEC (Shingella spp.)], enteropathogenic *E. coli* [EPEC (bfp1 & eae)], enterotoxigenic *E. coli* [ETEC (LT, STh, & STp)], and Shiga toxin (stx1 & stx2) producing *E. coli*; *Campylobacter* pan. & *Entamoeba* pan.; *Aeromonas* spp., *Cryptosporidium* spp., *Encephalitozoon* spp., & *Schistosoma* spp.; adenovirus (serotypes 40 and 41), astrovirus, Epstein-Barr virus (EBV), norovirus (GI/GII & GI.1/GII.4), rotavirus, and sapovirus; antibiotic resistance genes, including: β-lactam (CTX-M, TEM, SHV), carbapenemases/carbapenems (KPC, NDM, MCR-1, OXA), macrolide (ermB, mphA), and quinolone (QnrA, QnrB1, QnrB4, QnrS).

be characterized using shotgun metagenomics to analyze bacterial DNA. Metagenomic data will be processed into abundance tables using R (R core team, 2021). Alpha and beta diversity parameters will then be computed and compared between treatment arms. A differential abundance analysis will be performed to identify bacterial taxa whose abundance is significantly altered by the milk- and peanut-free RUTF relative to the standard RUTF.

Fecal samples will be collected for storage for these later analyses of the interventions' effects on gut health biomarkers at a sub-set of 5 of the study health centers (approximately 60 children per study arm, to total 180 children with SAM).

All SAM children at these 5 sites will be asked to a whole stool sample. For whole stool collection, the caregiver will be provided with a diaper and an adhesive urinary bag to prevent contamination by urine, and asked to wait until the child passes a stool, for a maximum of 4 hours after arrival. When the child passes a stool, the stool will be aliquoted into cryotubes and stored in a cooler bag immediately (within 15 minutes of collection), before being transferred to storage with liquid nitrogen or long-term storage at -80° C within 2 hours of collection. Further details on stool collection procedures are documented in the annexed SOP (see Annex 3).

Fecal samples will be collected at three timepoints: at baseline (initiation of treatment), at discharge from treatment, and at 3-months post-discharge. The baseline sample collection will occur before administration of antibiotics.

Table 7. Study procedures and data collection schedule

	Treatment course													Post-treatment										
	Wk 0*	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12**	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21	Wk 22	Wk 23	Wk 24
Determination of eligibility																									
Informed consent																									
Clinical evaluation***																									
Costing caregiver questions (subset)																									
Anthropometry***																									
Monitoring of adverse events ***																									
Capillary blood collection																									
Stool collection (subset)																									

*Initiation of wasting treatment

**Discharge from wasting treatment (approximately week 12)

***Follow up will be bi-weekly for MAM children and weekly for SAM children in accordance with national guidelines

Data management and confidentiality

Data will be collected by study staff at the study sites using standardized questionnaires and entered by study staff into electronic data capture system (Survey Solutions). Data will be regularly checked by designated staff for quality assurance. This electronic data capture system will be password-protected, secure, and only accessed by qualified study staff. Documents with identifiable information such as consent forms will be stored securely at the study office and accessed only by qualified study staff. All data collection will be directed by SOPs which will be developed and finalized prior to initiation of enrollment.

Statistical analysis

All analyses will be delineated in detail in the trial Statistical Analysis Plan (SAP) which will be developed and finalized prior to initiation of enrollment. A summary is given here.

The study is powered for separate comparisons between (i) the control group and SMS-RUTF, and (ii) between the control group and S-RUTF. All analyses will be stratified by MAM vs SAM status.

Baseline characteristics will be assessed with descriptive statistics (means and standard deviations for continuous variables, and proportions for categorical variables). Baseline characteristics will be adjusted for in the analyses if it is both (i) associated with treatment outcomes or relapse in published literature and (ii) imbalanced between treatment arms as determined by statistically significant t-test or χ^2 tests with 5% significance level.

For binary outcomes, we will use log-binomial regression to estimate relative risks (RRs) and 95% confidence intervals (CIs) for the RRs, adjusting for any baseline factors as appropriate. Non-inferiority will be declared if the lower bound of a one-sided 95% CI for the RR lies entirely below the non-inferiority margin of a relative 12.5%. For continuous outcomes, we will use linear regression to estimate differences in that outcome between treatment arms, adjusting for any baseline factors as appropriate. For superiority analyses (relapse), we will use a two-sided 95% CI and superiority will be declared if the lower bound of the 95% CI for the relative risk is above 1.0.

Non-inferiority analyses can be spuriously favored by ITT analyses because non-compliance diminishes any treatment effects, thus biasing the effect size toward the null (35). We will therefore repeat all non-inferiority analyses with a per-protocol (PP) population, restricting the analyses to only children who comply with their full treatment course, per caregiver report. The ITT and PP results will be presented side-by-side for non-inferiority analyses; superiority analyses will be analyzed as ITT only.

Adverse event (AE) and serious adverse event (SAE) monitoring and reporting

AEs and SAEs will be closely monitored and addressed in both study arms through the routine monitoring of children under wasting treatment, through weekly in-facility visits for SAM children and bi-weekly for MAM, as per national guidelines. AEs/SAEs will be documented in detail and reported to the study leadership. We will ensure the child receives appropriate medical care and monitoring as per guidelines. Definitions of AEs and SAEs are delineated in the annexed SOP (see Annex 4), where procedures are also documented in further detail.

A Data Safety and Monitoring Committee (DSMC) will be formed prior to initiation of enrollment to monitor SAEs, to review the protocol, and evaluate the statistical analysis plan. The DSMC will consist of a professor in pediatrics with experience in child wasting, a professor in epidemiology, and a statistical analysis expert. Monthly AE/SAE summaries will be compiled and sent to the chair of the DSMC. In case of a disproportional rise in monthly SAEs, the chair will convene the DSMC to decide whether the trial should be halted. Given the short character of the trial, there will be no interim analysis.

Early withdrawal from the study

While the study team intends to follow all participants from admission to treatment until 3 months post-discharge from treatment, participants have the option to withdraw from the study at any time for any reason, in accordance with the principles of voluntary participation (outlined in more detail in the section on Ethics below). A participant may be withdrawn from the study by the principal investigator (who will be blinded to treatment allocation) if they believes it is in the participant's best interest to do so. The reason for early withdrawal will be documented in the participant's study file, and if the withdrawal is due to an SAE, prompt medical treatment will be ensured.

Ethics

The study protocol will be submitted for review to the Institutional Review Boards (IRBs) of IFPRI (Washington DC, USA), and the Burkina Faso National Ethics Committee. In accordance with IFPRI requirements, all IFPRI staff participating in the study will have completed the Collaborative Institutional Training Initiative (CITI Program) basic training "Social and Behavioral Research", which addresses research ethics issues in data collection, analysis, and management. The entire data collection team will be trained in, and bound by, the basic ethical principles as outlined in the Declaration of Helsinki (36).

Community engagement

The research team will inform local and regional health authorities and community representatives of the research. In each locality in the study area, representatives of the research team will present the objectives and procedures of the study to the village authorities.

Voluntary and informed participation

The purpose and procedures of the study will be explained to all caregivers of eligible children in their local language through an information sheet. All respondents reserve the right to refuse to participate in the study and to withdraw from the study at any time, for any reason. Each interviewer will be asked to read the consent statement in its entirety, slowly and in the participant's local language so that they can understand it. They will then ask if the consent statement has been understood and if there are any questions. Consent for children will be given by a parent or legal guardian. An informed consent form will be signed by the child's primary caregiver or legal guardian, and, if present, the heads of the household.

Risks and benefits

There are no known risks related to the data collection through questionnaires or anthropometry. The child may feel some pain with the finger prick for capillary blood collection, and there is a slight chance of bruising. There are no direct benefits to the participants for participating in the study. There is an indirect benefit to the participants by the generation of evidence that may serve to benefit the community.

AE/SAE response

In the event of a medical problem (AE/SAE) that occurs or is identified during the assessment visits, all study participants will receive medical care. We will ensure that participants' medical care expenses are covered, whether by the Burkina Faso health care system or by the study insurance.

Participant privacy and confidentiality

Every precaution will be taken to ensure the anonymity of participants during data collection, data management, data analysis and dissemination of results. Completed questionnaires will be stored on a secure server accessible only to the study team. All databases will be made anonymous using identification codes. No personally identifiable data will be shared outside the survey team or kept in the de-identified databases.

Trial registration

The trial will be registered with clinicaltrials.gov and any modifications to the study protocol or consent forms will be submitted for ethical approval before implementation.

Record keeping and Trial Master File (TMF) management

The TMF will be managed electronically by the investigator and investigator-sponsor team, in compliance with the ethical principles outlined above for participant privacy and confidentiality. The electronic TMF will be stored securely, will be password-protected, and will be accessed only by study staff. Prior to enrollment, the investigator and investigator-sponsor team will prepare and keep updated all documents. Written approval of the principal investigator will be obtained before destroying the TMF. The TMF will include, but not be limited to, the following documentation:

- Approved protocol and any modifications, and all former versions
- Current questionnaire forms
- Insurance policy records
- Signed and dated curriculum vitae of all investigators and study personnel
- Approved informed consent forms in French and English, and all former versions
- SAE reports
- Investigators brochure and certificates of Good Manufacturing Practices for the interventional RUTF products
- Signed SOPs
- Budget details and financial aspects
- Statistical Analysis Plan
- Syntax for data quality checks
- Staff delegation logs
- Communication plan

Dissemination

We will disseminate results from this research in peer-reviewed journals, at scientific conferences, and through stakeholder meetings to relevant study partners.

Timeline summary

The trial is slated to begin enrolling in October 2024, with final follow-up visits occurring in October 2025 (Table 8). Primary analyses will be complete by February 2026.

Table 8. Chronology of the study

	Y1				Y2				Y3
Timeline	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
Protocol development and ethical review									
Production and shipment of RUTF									
Enrollment									
Recovery from SAM/MAM									
Post-recovery follow up									
Analysis of fecal samples									
Data analysis									
Manuscript writing									

Budget summary

This study is funded by the Japan Ministry of Foreign Affairs and UNICEF supply division.

Table 9. Budget summary by line item category

Line item		Amount
	Personnel	$573,815
	Training	$27,085
	Compensation for study participants	$45,627
	Insurance	$25,424
	Screening campaigns	$11,864
	Supplies including software and transport for supplies	$292,954
	Publication and dissemination	$7,100
	Meetings and sensitization	$3,220
	Travel and local transport for staff	$69,246
	Service charges	$123,752
	Institutional overheads	$275,947
Total		$1,456,034

Roles of investigators

	Contact information	Role
Investigator	IRSS 01 BP 2779 Bobo-Dioulasso, Bobo-Dioulasso Burkina Faso Phone: +226 50 36 32 15 - Laeticia Toe (Principal investigator): laeticiatoe@gmail.com - Trenton Dailey-Chwalibog: Trenton.Daileychwalibog@UGent.be	- Principal investigator and co-investigator of this research - Guarantor of the research protocol - Oversight of study implementation - Quality control of data collection - Dissemination of results
Implementing Agency	AfricSante 01 BP 298 Bobo-Dioulasso 01 Street 15.144, Bobo-Dioulasso 01, Burkina Faso Phone: +226 20 98 63 68 - Director Moctar Ouedraogo: bmoctar@gmail.com - Clinical research Coordinator: Dr Alain Hien: alain.hien1@gmail.com	- Research implementation and data collection
Investigator-Sponsor	IFPRI 1201 I St, NW, Washington, DC 20006-1002 USA Phone: +1 202-862-5600 Fax: +1 202-467-4439 Email: - Rebecca Brander: R.Brander@cgiar.org - Lieven Huybregts: L.Huybregts@cgiar.org - Jef Leroy: J.Leroy@cgiar.org IFPRI Dakar Title 3396, Lot #2 BP 24063 Dakar Almadies Senegal Phone: +221 33 869 9800 Email: - Talla Fall: T.Fall@cgiar.org	- Co-investigator - Guarantor of the research protocol - Statistical analysis plan - Oversight of study implementation - Quality control of data collection - Dissemination of results
Funding sponsors	• The Ministry of foreign affairs of Japan, represented by Mr Futoshi Yamauchi F.Yamauchi@cgiar.org • UNICEF - Alison Fleet: afleet@unicef.org - Sondos Mubarak: smubarak@unicef.org	Grantor

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