Efficacy of alternative RUTFs for treatment of child wasting and prevention of relapse: Statistical Analysis Plan

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List of acronyms

ABC-I	Activity-based costing–ingredients
AE	Adverse event
ALR	Additive log-ratio
ANCOM-BC2	Analysis of Composition of Microbiomes with Bias Correction 2
ANOVA	Analysis of variance
CACE	Complier Average Causal effects
CI	Confidence interval
CLR	Centered log-ratio
CMAM	Community Management of Acute Malnutrition
CONSORT	Consolidated Standards of Reporting Trials
CSPS	Centre de Santé et Promotion Sociale
DALY	Disability-adjusted life year
DSMB	Data Safety and Monitoring Board
ELISA	Enzyme-linked immunosorbent assay
GDP	Gross domestic product
HAZ	Height-for-age Z-score
ICC	Intra-class correlation coefficient
IFPRI	International Food Policy Research Institute
IRB	Institutional Review Board
IRSS	Institut de Recherche en Sciences de la Santé
IQR	Interquartile range
ITT	Intention-to-treat
LAZ	Length-for-age Z-score
LMM	Linear mixed model
LOS	Length of stay
MaAsLin2	Multivariate Association with Linear Models 2
MAM	Moderate Acute Malnutrition
MUAC	Mid-upper arm circumference
PERMANOVA	Permutational multivariate analysis of variance
RR	Relative risk
RUSF	Ready-to-use supplementary food
RUTF	Ready-to-use therapeutic food
SAE	Severe adverse event
SAM	Severe Acute Malnutrition
SAP	Statistical analysis plan
SD	Standard deviation
SMS-RUTF	Soy–maize–sorghum–based ready-to-use therapeutic food
SOP	Standard operating procedure
S-RUTF	Soy-based ready-to-use therapeutic food
UniFrac	Unique fraction distance metric
WAZ	Weight-for-age Z-score
WHO	World Health Organization
WHZ	Weight-for-height Z-score
WLZ	Weight-for-length Z-score

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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 non-inferiority of these formulations compared to the most commonly used milk- and peanut based RUFTF on recovery rates and to what extent recovery is sustainable. Sustainable recovery implies a lower rate of post-treatment relapse. In this study we evaluate two novel RUTF formulations, one that is peanut and milk-free based on soy, maize and sorghum (SMS-RUTF) and one with reduced milk based on soy (S-RUTF).

Hypotheses and Objectives

Main trial

1. To assess the non-inferiority of novel soy-maize-sorghum (SMS-) RUTF and soy-based (S-) RUTF on treatment recovery to standard RUTF
    Hypothesis: MAM and SAM children who received SMS-RUTF or S-RUTF during treatment will have non-inferior recovery rates, compared to those who received standard RUTF.
2. To assess the superiority of SMS-RUTF and S- RUTF on post-recovery relapse compared to standard RUTF
    Hypothesis: MAM and SAM children who received SMS-RUTF or S-RUTF during treatment will have lower relapse rates compared to children who received standard RUTF.

Sub-study 1: Acceptability

1. To assess the acceptability of S-RUSF and SMS-RUSF in MAM children
    Hypothesis: SMS-RUTF and S-RUTF will each have similar acceptability compared to standard RUTF
2. To assess the sensory adaptation to the products
    Hypothesis: The children adapt to the product with increased intake over time.

Sub-study 2: Microbiome and gut health

1. To evaluate the association between intestinal, inflammation microbiome composition and enteropathogen burden (collectively referred to as “gut health” in this document) and relapse rates in children with SAM treated with SMS-RUTF, S-RUTF, or standard RUTF.
    Hypothesis: Improved gut health will be associated with lower relapse rates in all treatment groups
    Improved gut health will be associated with lower relapse rates in children treated with SMS-RUTF and S-RUTF compared to those receiving standard RUTF
2. To assess the impact of SMS-RUTF and S-RUTF gut health, relative to standard RUTF, in children with SAM.

Hypothesis: SMS-RUTF and S-RUTF will have a more favorable impact on gut health compared to standard RUTF in children with SAM.

Sub-study 3: Costing

1. To estimate the cost-efficiency and cost-effectiveness SMS-RUTF, S-RUTF, and standard RUTF
   Hypothesis: Not applicable as no statistical hypothesis testing will be done.

Study methods

Study setting

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 (1). Burkina Faso has seen deteriorating humanitarian conditions since 2020, with numbers of internally displaced persons exceeding 2 million due to security incidents, and increasing populations of 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

Main trial

This will be a facility-based, triple blinded individually randomized controlled trial with three arms, including two interventions and one control arm, with a 1:1:1 allocation ratio. Children will be enrolled upon initiation of MAM or SAM treatment and followed monthly for 3 months post-discharge from treatment.

Sub-study 1: Acceptability

In a sub-set of facilities, we will conduct a 3x3 full Latin square crossover design to evaluate acceptability of the two products to address objective 1 (acceptability of S-RUTF and SMS-RUTF) and assess the adaptation to the products to address objective 2 (sensory adaptation). The 3x3 full Latin square crossover design will involve measurements of the RUSFs' observed intakes at four time points — baseline (day 1), day 8 (product switching), day 15 (product switching), and day 22.

Sub-study 2: Microbiome and gut health

In a subset of facilities, fecal samples will be collected at baseline (admission), discharge, and 3 months post-discharge or upon relapse within 3 months after discharge from treatment.

Sub-study 3: Costing

We will employ an activity-based costing-ingredients (ABC-I) approach to collect and analyze data on costs incurred in each treatment arm. This approach involves documenting all costs and allocating them to the activity in which they were incurred. Both societal and health system perspectives will be used. The health system perspective includes only costs to the health system, whereas the societal perspective includes health system costs as well as expenses and opportunity costs to caregivers (2,3). This will include costs and opportunity costs to caregivers.

Study interventions

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)
- **SMS-RUTF (intervention 1)**: a milk- and peanut-free product with added crystalline amino acids that provide significantly more fiber (~5.0g per 100g)
- **S-RUTF (intervention 2):** a reduced-milk product

Burkina Faso national guidelines for MAM and SAM ambulatory treatment will be followed for dosing the products and all other aspects of treatment (4). Thus, all children will receive the standard of care for Community Management of Acute Malnutrition (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 (4). Briefly, upon admission to treatment for SAM, children will undergo medical evaluation and appetite test and receive routine antibiotics and rapid diagnostic test for malaria as well as other treatments as indicated in the guidelines. Caregivers of eligible children will be provided with RUTF and instructed on how 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 for a maximum of 12 weeks and will be eligible to be discharged when they have achieved anthropometric recovery (see definition below). 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.

Study eligibility and recruitment

Main trial

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 mid upper arm circumference (MUAC) ≥ 11.5 and < 12.5 cm, or weight-for-length/height z-score (WLZ/WHZ) ≥-3 and < -2 and absence of bilateral pitting edema. Uncomplicated SAM (i.e., cases of SAM that are eligible for ambulatory treatment) will be defined by all the following criteria: (i) MUAC < 11.5 cm or WLZ/WHZ < -3, (ii) no clinical complications, (iii)absence of bilateral pitting edema, and (iv) 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 (4)).

The inclusion criteria for MAM ambulatory treatment are:

- Age 6-59 months
- 11.5 cm ≤ MUAC < 12.5 cm, or -3 ≤ WLZ/WHZ < -2
- Absence of clinical complications
- Absence of bilateral pitting edema

- Pass the appetite test
- Accompanied by caregiver or legal guardian
- Caregiver or legal guardian consents to participate

The inclusion criteria for SAM ambulatory treatment are:

- Age 6-59 months
- MUAC < 11.5 cm, or WLZ/WHZ < -3
- Absence of clinical complications
- Absence of bilateral pitting edema
- Pass the appetite test
- Accompanied by caregiver or legal guardian
- Caregiver or legal guardian consents to participate

The exclusion criteria for MAM or SAM ambulatory treatment are therefore:

- Acute malnutrition requiring hospitalization (presence of clinical complications, failure to pass the appetite test, or presence of bilateral pitting edema)
- Known allergy to any of the ingredients in the RUTF products
- Already enrolled in MAM or SAM ambulatory 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 will be screened for eligibility upon presentation at the study health centers, and will be determined to be eligible upon diagnosis with uncomplicated MAM or SAM.

Sub-study 1: Acceptability

This nested sub-study will recruit children with MAM at a sub-set of 5 of the 30 study facilities in the main trial. Inclusion criteria for this sub-study therefore include age 6-59 months, MUAC < 125 mm and ≥ 115 mm, or WLZ/WHZ < -2 and ≥-3, absence of clinical complications, passing the appetite test, accompanied by caregiver or legal guardian, and caregiver consent. Exclusion criteria include presence of SAM, requiring hospitalization, known RUTF ingredient allergies, already enrolled in a MAM or SAM treatment program, physical abnormalities that cause measurement issues, or plans to move away within six months.

Sub-study 2: Microbiome and gut health

This nested sub-study will recruit children with SAM at a sub-set of 5 of the 30 study facilities in the main trial. Inclusion criteria for this sub-study therefore include age 6-59 months, MUAC < 115 mm or WLZ/WHZ < -3, absence of clinical complications, passing the appetite test, accompanied by caregiver or legal guardian, and caregiver consent. Exclusion criteria include needing hospitalization, known RUTF ingredient allergies, already enrolled in a MAM or SAM treatment program, physical abnormalities that cause measurement issues, or plans to move away within six months.

Sub-study 3: Costing

This nested sub-study will have the same population as the main trial, i.e., children 6-59 months old with MAM or uncomplicated SAM presenting to the study facilities. In all study facilities, we will observe at least one visit for a child at each of the 30 study facilities for documenting staff time allocations. We will collect caregiver cost information from the caregivers participating in the acceptability sub-study.

Study ethics summary

The study protocol was approved by the Institutional Review Boards (IRBs) of IFPRI (Washington DC, USA), and the Burkina Faso National Ethics Committee. The study was registered on clinicaltrials.gov (identifier: NCT06912620). Caregivers or legal guardians of eligible children will undergo informed consent, and all participant data will be collected and stored confidentially. All sub-studies were included in the main study protocol.

Controls

Blinding

This study will be triple blinded; that is, the study investigators, participants, and outcome data collectors will be blinded to randomization assignment. The study products will have identical packaging, and will be stored in boxes that are identically labeled to the extent possible. The products will be identified only with one of three alphabet letters, and the codes to these alphabet letters will not be accessible by the study team until after analyses are completed. While the participants will technically be blinded to their treatment assignment, the products will likely differ in their taste and appearance, meaning that true blinding for participants may not be possible due to the nature of their different recipes. However, we expect concerns of bias due to this to be minimal.

Method of treatment assignment/randomization

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 blocks of 45. Without the investigators' knowledge, the producers will be informed which letters to print on the package of each supplement. Information regarding the assignment of the letter codes to the intervention and control supplements will be stored electronically by the director of Nutrition, Diets and Health unit of IFPRI, inaccessible by the investigators, until analysis is completed.

Eligible children will be randomly assigned to one of the three study groups at study inclusion. The study staff will open the sealed envelope corresponding to the next sequential participant identification number in the presence of an eligible mother-child pair (in order of arrival) and will provide them with the RUTF supplement according to the letter code. The participant's number, as well as the letter code, will be recorded on the study participant's card, their medical records, and scanned into the electronic data capture system.

Study outcomes

Main trial

The primary and secondary outcomes for the main trial and their definitions are listed in Table 1. Outcomes are the same for MAM and SAM children.

Table 1. Primary and secondary efficacy 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, at the day of end of treatment	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
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 the day of end of treatment	Non-inferiority
Anthropometry at discharge from treatment	WLZ/WHZ, MUAC, weight, height/length, LAZ/HAZ and WAZ at the day of end of treatment	Non-inferiority
Anthropometry at 3-months post-discharge	WLZ/WHZ, MUAC, weight, height/length, LAZ/HAZ and WAZ at 3-months post-discharge (3 months after the day of end of treatment)	Superiority
Hemoglobin at discharge	Hemoglobin concentration (grams/liter) at the day of end of treatment	Non-inferiority
Hemoglobin at 3-months post-discharge	Hemoglobin concentration (grams/liter) at 3-months post-discharge (3 months after the day of end of treatment)	Superiority
Secondary outcomes		
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. As per the Burkina Faso national protocol, children are to be transferred to inpatient care if they meet any of the following criteria: negative appetite test, weight loss for 3 consecutive visits, stagnant weight for 4 consecutive visits if all other social and nutritional reasons have been addressed, onset of clinical condition (edema, fever, hypothermia, severe dehydration, repeated or incessant vomiting, severe respiratory problem, very pale with difficulty breathing, severe malaria,	Non-inferiority

	abscesses or extensive skin lesions, weakness or unconsciousness, convulsions or malaise) (4).	
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. Children who are non-responders are referred to inpatient care as per Burkina Faso guidelines.	Non-inferiority
Adherence to treatment services	Caregiver attends the recommended schedule of visits and receive RUTF supply	Non-inferiority
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 signs or diagnoses	Indication of morbidity on health center card	Non-inferiority
Anemia at discharge	Hemoglobin concentration < 105 gram/liter for children 6-23 months of age or < 110 gram/liter for children 24-59 months of age, at discharge	Non-inferiority
Anemia at 3-months post-discharge	Hemoglobin concentration < 105 gram/liter for children 6-23 months of age or < 110 gram/liter for children 24-59 months of age, at 3-months post-discharge	Superiority
Mortality	Death at any time during treatment or during the post-discharge follow-up period	Non-inferiority

Sub-study 1: Acceptability

The primary and secondary outcomes for the acceptability study and their definitions are listed in Table 2.

Table 2. Primary and secondary acceptability outcomes

Outcome type	**Outcome definition**
Primary	Observed dose intake/ consumed (g) after one week trial
Secondary	Adaptation effect (difference between observed dose intakes on first day and after one week trial)
Secondary	Reason for ending test dose (refusing the product)
Secondary	Proportion of empty sachets returned relative to the number of sachets received one week before (adherence indicator)
Secondary	Caregiver-reported product sharing (binary adherence indicator)
Secondary	Caregiver-reported number of times per day the product was consumed at home (intake frequency)
Secondary	Perceived liking scores (by caretakers) according to Likert scale
Secondary	Product ranking/selection (by mothers)

Secondary	Food frequency changes during each product trial
Secondary	Breastfeeding frequency during each product trial
Secondary	Caregiver-reported presence of an adverse effect (diarrhea, vomiting…)

Sub-study 2: Microbiome and gut health

The primary outcome of this study is species richness, measured through shotgun metagenomics. Secondary outcomes include inflammation markers, enteropathogen burden, and microbiome composition. Inflammation markers (α-1 antitrypsin, lipocalin-2, fecal neopterin, myeloperoxidase) will be analyzed via enzyme-linked immunosorbent assay (ELISA) kits. Enteropathogen burden and microbiome composition will be assessed using TaqMan Array Card assays and shotgun metagenomics, respectively.

Sub-study 3: Costing

Outcomes for the costing study are listed in Table 3.

Table 3. 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
Cost per treated SAM child recovered	Cost-effectiveness	Total cost of SAM treatment divided by the number of SAM children recovered during that period

Sample size and statistical power

Main trial

We estimate a total sample size of 1080 children with SAM (360 per arm) and 1080 children with MAM (360 per arm) will provide sufficient statistical power to demonstrate non-inferiority for each comparison, with a non-inferiority margin of relative 12.5%, assuming a recovery rate in the control of 76% and a loss to follow up of 15% (Table 4). The sample size will be smaller for analyses of relapse, 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, $\beta = 0.8$, and 15% attrition[1]. While the key objectives of this research are to evaluate effects of the alternative RUTFs on recovery and relapse, we consider as primary outcomes any outcome for which we have adequate power for clinically or policy meaningful effect sizes (5).

[1] Stata commands ssi for continuous outcomes and artbin for binary outcomes were used for non-inferiority analyses, and power twomeans for continuous outcomes and power twoproportions for binary outcomes were used for superiority analyses. Outcome proportions, means, or standard deviations were taken from relevant studies in literature as delineated in Table 4.

Table 4. Calculations of detectable effect sizes for all outcomes

Outcome	Outcome prevalence in the literature	Type of analysis	Non-inferiority margin (relative) with ≥80% power (Non-inferiority)	Detectable effect size at 80% power (Superiority)	Rank of outcome
Anthropometric recovery at discharge	MAM recovery (with RUSF*): 73% (6); 73% (7); 85% (8) SAM recovery: 55.4% (9); 82.3% (10); 76% (11); 71% (pooled estimate from meta-analysis) (12)	Non-inferiority	12.5% relative margin		Primary
Relapse to wasting within 3-months post-discharge	Post-MAM relapse: 30% within 3 months (13); 33% within 12-months (14) Post-SAM relapse: 6.8% 3-month cumulative incidence (15); 24% 2-month cumulative incidence (16); 30% within 3-months (unpublished)	Superiority		Risk difference of 11%; Relative risk = 0.72	Primary
Length of stay (LOS) among recovered children	MAM: 36.4 days (SD 50.4 days)(17); 5.9 weeks (95% CI: 4.9, 7.0)(18) SAM: 56 days (assumed 41 day SD) (9)	Non-inferiority	MAM: 4.9 days; 12.5% relative margin SAM: 8 days; 12.5% relative margin		Primary
Weight gain during treatment	MAM: 4.1 g/kg/day (SD = 3.0) (17), SAM: 3 g/kg/day (SD = 4.7) in 6-23 mo and 8.6 g/kg/day (SD = 4.7) in 24-59 mo (19)	Non-inferiority	MAM: 0.14 kg; 12.5% relative margin SAM: 0.91 g/kg/day; 12.5% relative margin		Primary
Anthropometry at discharge from treatment	MAM: All estimates from Fabiansen et al (20) WLZ: -1.52	Non-inferiority	MAM:		Primary

	MUAC: 130.1 mm HAZ: -1.86 WAZ: -2.6 (assumed from SAM because estimates not available) Weight: 7.8 kg Height: 72.9 cm SAM: All estimates from Kangas et al(9) WLZ: -1.9 MUAC: 125.9 mm HAZ: -2.3 WAZ: -2.6 Weight: 7.3 kg Height: 71.6 cm		WLZ: 0.2 z-scores; 12.5% relative margin MUAC: 6.8 mm; 5% relative margin HAZ: 0.2 z-scores; 12.5% relative margin WAZ: 0.4 z-scores; 12.5% relative margin Weight: 0.4 kg; 5% relative margin Height: 3.8 cm; 5% relative margin SAM: WLZ: 0.3 z-scores; 12.5% relative margin MUAC: 6.3 mm; 5% relative margin HAZ: 0.3 z-scores; 12.5% relative margin WAZ: 0.4 z-scores; 12.5% relative margin Weight: 0.4 kg; 5% relative margin Height: 3.8 cm; 5% relative margin		
Anthropometry at 3-months post-discharge	MAM: All estimates from Fabiansen et al (20)	Superiority		MAM: WLZ: 0.26	Primary

	WLZ: -1.52 MUAC: 130.1 cm HAZ: -1.86 WAZ: -2.6 (assumed from SAM because estimates not available) Weight: 7.8 kg Height: 72.9 cm SAM: All estimates from Kangas et al(9) WLZ: -1.9 MUAC: 125.9 cm HAZ: -2.3 WAZ: -2.6 Weight: 7.3 kg Height: 71.6 cm			MUAC: 2.46 cm HAZ: 0.39 WAZ: 0.37 Weight: 0.39 kg Height: 1.87 cm SAM: WLZ: 0.37 MUAC: 3.13 cm HAZ: 0.48 WAZ: 0.37 Weight: 0.55 kg Height: 2.76 cm	
Hemoglobin at discharge	MAM: 108 g/L (SD = 13) (21) SAM: 108.6 g/L (SD = 11.2) (22)	Non-inferiority	MAM: 2.7 g/L; 2.5% relative margin SAM: 2.2 g/L; 2.5% relative margin		Primary
Hemoglobin at 3-months post-discharge	MAM: 108.0 g/L (SD = 13) (21) SAM: 108.6 g/L (SD = 11.2) (22)	Superiority	--	MAM = 2.9 g/L SAM = 2.9 g/L	Primary
Default from treatment	MAM: 6.8% (17) SAM: 8.5% (9)	Non-inferiority	MAM: 50% relative margin SAM: 45% relative margin		Secondary
Transfer to inpatient treatment	MAM: 5.8% (20) SAM: 20.1% (9)	Non-inferiority	MAM: 70% relative margin SAM: 40% relative margin		Secondary
Non-response to treatment	MAM: 32.2% (18), 28%(20) SAM: 12.5% (9)	Non-inferiority	MAM: 30% relative margin SAM: 25% relative margin		Secondary

Compliance to treatment services (attendance at visits)	MAM: 87% (17) SAM: 11.1% (11)	Non-inferiority	MAM: 50% relative margin SAM: 10% relative margin		Secondary
Relapse to SAM	Note: Reporting of relapse as MAM vs SAM is not common. Daures et al reported 88.6% of relapses were MAM (23), so we apply this proportion to the below rates. Post-MAM relapse to SAM: 30% within 3 months (13); 33% within 12-months (14) Post-SAM relapse to SAM: 6.8% 3-month cumulative incidence (15); 24% 2-month cumulative incidence (16); 30% within 3-months (unpublished)	Superiority		MAM and SAM (Assumed to be same): RR = 0.34	Secondary
Relapse to MAM	Note: Reporting of relapse as MAM vs SAM is not common. Daures et al reported 88.6% of relapses were MAM (23), so we apply this proportion to the below rates. Post-MAM relapse to SAM: 30% within 3 months (13); 33% within 12-months (14) Post-SAM relapse to SAM: 6.8% 3-month cumulative incidence (15); 24% 2-month cumulative incidence (16); 30% within 3-months (unpublished)	Superiority	-	MAM and SAM (Assumed to be same): RR = 0.689	Secondary
Morbidity	MAM: 61.1% (any illness) (17) SAM: 60.0% (any illness) (9)	Non-inferiority	MAM: 17.5% relative margin SAM: 17.5% relative margin		Secondary

Anemia at discharge	MAM: 49% prevalence (21) SAM: 51% prevalence (22)	Non-inferiority	MAM: 17.5% relative margin SAM: 17.5% relative margin	--	Secondary
Anemia at 3-months post-discharge	MAM: 49% prevalence (21) SAM: 51% prevalence (22) *estimates are sourced from studies presenting data at discharge because post-discharge data not available	Superiority	--	MAM: 23.3% relative SAM: 24.2% relative	Secondary
Mortality		Non-inferiority			Exploratory

Sub-study 1: Acceptability

A total sample size of 102 children was targeted based on recommendations in UNICEF protocols for acceptability testing of novel RUTF products, the requirement for complete sequences in a 3×3 full Latin square crossover design, and statistical power considerations. The sample size is consistent with the statistical power considerations, assuming a non-inferiority margin of 4 grams per observed intake in 30 minutes from a test dose, a between-subject standard deviation (SD) of 6.75 grams per kilogram body weight from literature, a conservative intra-class correlation (ICC) of 0.3, and an overall alpha (two-sided) of 0.05 (translating to a one-sided alpha of 0.025 for a non-inferiority test), 90% power, and attrition rate of 20%.

Sub-study 2: Microbiome and gut health

We calculated the required number of participants based on expected species richness indices from a rural Gambian cohort study that compared interactions between the fecal gut microbiome, enteric pathogens, and energy-regulating hormones among acutely malnourished children (24). We anticipate a species richness index of 49 (SD ± 23) in relapse cases (equivalent to Gambian children with SAM) and 64 (SD ± 27) in non-relapse cases (equivalent well-nourished Gambian children). Using a significance level of 0.05 and a desired power of 80%, we estimated a sample size of 44 participants per group. The effect size, a difference of 15 in species richness, is clinically meaningful and is justified by the study conducted in Gambia. We expect relapse to occur in 10% of children in Burkina Faso, and thus a total sample of 489 recruited children will likely yield 44 cases of relapse, accounting for 10% loss to follow up.

Sub-study 3: Costing

As the goal of the costing study is descriptive and no statistical hypothesis testing will be conducted, the sample size is not based on statistical power calculations. Rather the sample size is based on concerns of feasibility and representativeness of the sample. The selected sample size is expected to lead to costing results that are representative of the costs for MAM and SAM treatment in these 30 health facilities and will be feasible to collect.

Statistical analyses

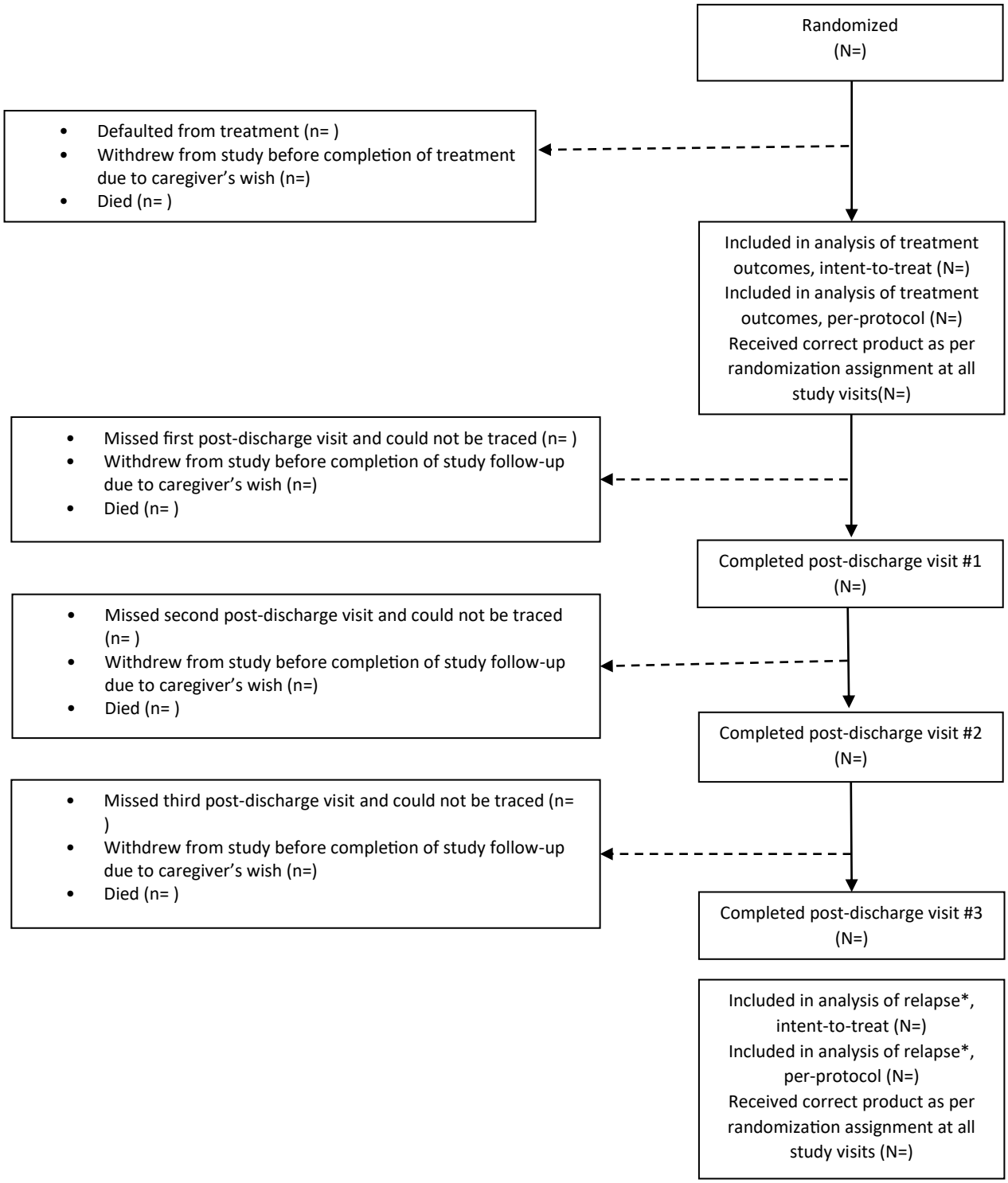
Main trial

All analyses will be reported as per CONSORT guidelines for randomized trials (25).

Study accrual

We will report the numbers of participants who were randomized, received intended treatment, and were included in the analyses for primary outcomes. These numbers will be presented in the format as depicted in Figure 1 consistent with the flow diagram required for CONSORT reporting.

Figure 1. Study accrual profile for the main trial



*Children will be included in analyses of relapse outcomes if they recovered and had at least one post-discharge visit

Statistical methods

We will conduct two separate comparisons between (i) the control group and SMS-RUTF, and (ii) between the control group and S-RUTF. All analyses will be done separately by wasting severity status (MAM vs SAM); that is, all analyses will be conducted and presented among MAM children and among SAM children separately. No adjustments for multiple comparisons will be made.

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 (described further below). If the regression model is adjusted, we will present both crude (unadjusted) and adjusted model results. If the models do not converge, we will use Poisson regression models with robust estimation of standard errors (26) and report which model was used. 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 superiority analyses, 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. All analyses will be adjusted for health center to reflect the stratified randomization (27–29).

For continuous outcomes measured at one timepoint, we will use linear regression to estimate differences in that outcome between treatment arms, adjusting for any baseline factors as appropriate and health center (as explained above). Both unadjusted and adjusted model results will be presented.

For any outcome for which non-inferiority is demonstrated, we will then sequentially test for superiority. In these cases, we will report both non-inferiority and superiority results. The superiority analysis will be considered exploratory, as the study power calculations were based on non-inferiority effect size.

We will conduct one sensitivity analysis. There were children enrolled near the end of the study whose product was switched to standard of care product during their treatment course because the expiration date of the study products occurred during their treatment course. That is, they received the study product to which they were randomized for the majority of their treatment course, and then when the expiration date of that product neared, they received a standard of care product for the remainder of their treatment duration. As these children received both the study and standard of care products, including them in the study arm to which they were randomized represents misclassification and their inclusion could bias the results to the null. If we were to exclude only the children assigned to the expiring product, there is the potential to induce bias by excluding children with long treatment durations or poorer treatment outcomes in one treatment arm, making treatment outcomes spuriously appear worse in this arm. Therefore, we will conduct a sensitivity analysis excluding all children in all treatment arms who received product on or after the date on which this switch was made.

Treatment of missing data

Wherever more than 10% of outcome observations are missing, we will report the number of observations used in the analysis. No imputation of missing data will be done, given the limited number of covariates available to predict missing observations. Every effort will be made to minimize attrition of study participants, thus keeping missing data to a minimum. Default from treatment will be considered a treatment outcome, rather than missing data.

Analysis frame

Our primary analysis frame will be intention-to-treat (ITT). ITT groups will be defined by the randomization assignment to which participants are allocated; that is, all participants will be included in the analysis based on the treatment group to which they were randomized.

However, ITT analyses can bias effect sizes toward the null, spuriously demonstrating non-inferiority, because non-compliance diminishes any treatment effects (30). Despite this, ITT is still the recommended approach for non-inferiority trials (31). To mitigate this concern, we will conduct a secondary analysis in which we repeat all analyses with a Complier Average Causal Effects (CACE) approach. CACE analyses adjust for any differences between children who adhere vs do not adhere in characteristics that may influence outcomes, thus mitigating concerns of confounding. CACE analyses are also useful for superiority analyses, as these results can distinguish between the effects of the interventions themselves, and effects of the adherence to the interventions. Both ITT and CACE results will be presented. This is summarized in Table 5.

Adherence will be defined as attendance at all treatment visits. The characteristics to be considered for adjustment and the decision rules to determine whether adjustment will be made will be the same as described in the next section below.

Table 5. Analysis approaches and sensitivity analyses by type

Analysis type	Primary analysis	Secondary analysis	Sensitivity analyses
Non-inferiority	ITT	CACE	Exclusion of children who received both study products and standard of care products during treatment course
Superiority	ITT	CACE	Exclusion of children who received both study products and standard of care products during treatment course

Baseline characteristics

Baseline characteristics (those that are ascertained at enrollment [admission into wasting treatment], before the treatment is administered) will be presented by treatment group and by wasting severity status. These characteristics will be assessed with descriptive statistics (means and standard deviations for continuous variables, and proportions for categorical variables). Baseline characteristics (sex, age and anthropometry at admission, caregiver-reported morbidities at admission, presence of morbidity as per health worker documentation [failed appetite test, fever (temperature ≥ 38 °C), high respiratory rates (50 breaths per minute for children up to 12 months or age; 40 breaths per minute for children 12 to 59 months), anemia and severe anemia (defined as above), skin condition, dehydration, oral candidiasis) 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 defined as a difference of at least 5% in absolute terms.

A shell table depicting the baseline information that will be available, and presented by treatment group, is presented in Table 6.

Table 6. Baseline characteristics that will be collected at study enrollment and presented by treatment group

		SMS-RUTF		S-RUTF		Control	
		MAM N=	SAM N=	MAM N=	SAM N=	MAM N=	SAM N=
Child/caregiver characteristics							
	Age at admission, mo (SD)						
	Male sex, %						
Wasting episode characteristics							
	WLZ at admission (SD)						
	WLZ < -2, %						
	MUAC at admission, mm (SD)						
	MUAC < 125 mm, %						
	Edema present, %						
	Type of admission						
	New case, %						
	Readmission, %						
	Relapse, %						
	Anemic, %						
	Hemoglobin, g/dL (SD)						

Interim analyses and data monitoring

No interim analyses will be done. Adverse events (AEs) and severe adverse events (SAEs) will be evaluated at every follow up visit during treatment (weekly for children with SAM and bi-weekly for children with MAM), and will be addressed and reported as per the study Standard Operating Procedures (SOPs).

A Data Safety and Monitoring Board (DSMB) will be convened prior to enrollment, who will monitor study progress and participant safety (including adverse events monitoring). Data reports will be prepared for the DSMB reporting the following:

- Study accrual profile and recruitment numbers by month
- Baseline characteristics
- Protocol violations
- Recovery and relapse rates
- Treatment outcomes
- (Serious) adverse events

The above data will be pooled across sites, blinded, and stratified by MAM vs SAM. All data will retain blinding at all times. No closed session (unblinded) reports will be done. No statistical testing will be done on any data reported to the DSMB; only descriptive data will be reported. A shell table depicting the outcome and adverse event summaries that will be sent to the DSMB for monitoring is depicted in Table 7. These monitoring reports will be sent to the DSMB prior to the DMSB meetings. The DSMB will meet after approximately 300 SAM children have treatment outcomes, or at the call of the DSMB chair or study investigators.

Table 7. Shell table of outcome and safety data to be monitored by DSMB

	MAM			SAM		
	Arm 1	**Arm 2**	**Arm 3**	**Arm 1**	**Arm 2**	**Arm 3**
Treatment outcomes						
	N with outcome data available =	**N with outcome data available =**	**N with outcome data available =**	**N with outcome data available =**	**N with outcome data available =**	**N with outcome data available =**
Recovered from treatment						
Death						
Default						
Non-response						
Referral						
Transfer						
Post-discharge outcomes						
	N with ≥ 1 post-discharge visit = **N of follow up visits =**	**N with ≥ 1 post-discharge visit =** **N of follow up visits =**	**N with ≥ 1 - post-discharge visit =** **N of follow up visits =**	**N with ≥ 1 post-discharge visit =** **N of follow up visits =**	**N with ≥ 1 post-discharge visit =** **N of follow up visits =**	**N with ≥ 1 post-discharge visit =** **N of follow up visits =**
Relapse within 3 months						
Adverse event data*						
	N with ≥ 1 follow up visit completed = **N of visits completed:**	**N with ≥ 1 follow up visit completed =** **N of visits completed:**	**N with ≥ 1 follow up visit completed =** **N of visits completed =**	**N with ≥ 1 follow up visit completed =** **N of visits completed:**	**N with ≥ 1 follow up visit completed =** **N of visits completed:**	**N with ≥ 1 follow up visit completed =** **N of visits completed:**
Anemia						

Adverse event (as per documentation by health center staff)	Severe anemia						
	Failed appetite test**						
	Fever**						
	Dehydration**						
	Skin condition**						
	Oral candidiasis**						
Serious adverse event (death or hospitalization***)	Death						
	Referral to inpatient care						
	Transfer to inpatient care						
Classification of serious adverse events (relatedness to intervention)	Unclassifiable or not assessable						
	Conditional or not classified						
	Improbable						
	Possible						
	Probable or plausible						
	Certain						

*Adverse event rates are reported as number of children with the event, divided by number of children with data available. For example, anemia rate is the number of children with anemia at least one follow up visit, divided by the number of children who had at least one follow up visit.

**Not recorded in the medical records for MAM children

***Including referral or transfer to inpatient care for wasting.

Treatment of inclusion and randomization errors

For ITT analyses, all children will be analyzed according to the treatment group to which they were randomized. For CACE analyses, children who did not attend all treatment follow-up visits will be considered as "non-adherent." Ineligible children who were erroneously enrolled will be handled as a protocol violation and will be removed from the study, and from the analysis. Ineligibility is defined above in the section entitled "Study Eligibility and Recruitment."

Sub-group and sensitivity analyses

We will conduct two *a priori* sub-group analyses for primary study outcomes only. These are for exploratory purposes, and our study did not factor these sub-groups into account in power calculations. We will assess all primary study outcomes separately among the following sub-groups of children:

1. Age group at enrollment: 6-23 months vs 24-59 months
2. Children with high-risk MAM, defined as MAM status at enrollment (defined as above) and any of the following characteristics:
    a. Age 6-23 months
    b. WAZ < -3
    c. MUAC 115-119 mm
    d. History of SAM
    e. Present case of MAM is a relapse case

We hypothesize the alternative RUTFs may have a different effect in these sub-groups. First, if the alternative RUTFs impact the gut microbiome of children, these interventions may have greater impact on the anthropometry outcomes of younger children. The gut microbiome before three years of age is especially sensitive to external influences such as nutrition, and thus may represent a critical window in which interventions may have the most influence (32). Conversely, one study on a previous formula of SMS-RUTF reported lower efficacy among children 6-23 months of age (33), although a subsequent study reported non-inferiority of the SMS-RUTF product among this age group after it had been reformulated (19). Further data on the efficacy of this product within the subgroup of 6–23-month-old children is useful.

Children with MAM or SAM have microbiome profiles that are more immature for their age and this deleterious microbiome immaturity is inversely associated with WHZ even within MAM or SAM categories (34). Thus, we hypothesize that children with high-risk MAM may have gut microbiome profiles that are more suboptimal than their lower-risk MAM counterparts, and thus may stand to experience a stronger benefit from any microbiome influences exerted by the products. Additionally, release of new WHO guidelines on the prevention and management of wasting in 2023 recommend prioritize specialized food products (such as RUTF) for high-risk MAM (35), and thus efficacy data within this sub-group may be useful for policymakers in Burkina Faso in implementing these guidelines in the coming years.

As described above, we will conduct one sensitivity analysis, in which we exclude children whose treatment product was switched to the standard RUTF before the expiration date of their treatment product.

Sub-study 1: Acceptability

We will evaluate balance in key demographics, anthropometry, health history, and dietary history, using descriptive statistics, and will adjust for the covariates listed in Table 8 as fixed effects in the outcome models if they are strongly correlated with the primary outcome. Outcomes will be analyzed using the methods specified in Table 9.

Table 8. Covariates to evaluate in the acceptability study

Variables	**Type of variable**	**Planned statistical analysis**
Demographics[1]		
Sex	Categorical (binary)	Descriptive count (%), covariate
Age (months)	Continuous	Descriptive means (SD) or medians (IQR), covariate
Mother age (years)	Continuous	Descriptive means (SD) or medians (IQR), covariate
Anthropometry[1]		
Weight (kg)	Continuous	Descriptive means (SD) or medians (IQR), covariate
Height (cm)	Continuous	Descriptive means (SD) or medians (IQR), covariate
MUAC (mm)	Continuous	Descriptive means (SD) or medians (IQR), covariate
Health history[1]		
Diagnosis of previous moderately acute malnutrition during the last 2 years	Categorical (binary)	Descriptive count (%), covariate
Experience of severe acute malnutrition during the last 2 years	Categorical (binary)	Descriptive count (%), covariate
Diagnosed illnesses during the last 3 months	Categorical (binary)	Descriptive count (%), covariate
Medication for a serious illness for the last 3 months	Categorical (binary)	Descriptive count (%), covariate
Dietary history[1]		
Food consumption frequency (during the last month)	Count	Descriptive count (%), covariate
Breastfeeding status at inclusion (Exclusive)	Categorical (binary)	Descriptive count (%), covariate
Average number of breastfeeding sessions per day during the last month	Count	Descriptive count (%), covariate
Appetite test		
Observed dose intake/ consumed (g) (day 1)	Continuous	Descriptive means (SD) or medians (IQR), covariate

[1] The parameters are weekly monitored during the study, and any occurrence of health degradation (illness or progression to SAM) will result in withdrawal from the study.

Table 9. Statistical methods for each outcome in the acceptability study

	Type of variable	Planned statistical analysis
Primary outcomes		
Observed dose intake/ consumed (g) (after product trial for 7 days)	Continuous	Descriptive means (SD) or medians (IQR), analyzed with Linear Mixed Model (LMM) regressions with sequence and period as fixed effects
Secondary outcomes		
Product adaptation (difference (Δ) between observed dose intakes (g) on day 1 and after a one-week trial)	Continuous	Descriptive Δ means (SD) or Δ medians (95% CI), analyzed with repeated-measures LMM (compound symmetry covariance) with sequence and period as fixed effects
Reason for ending test dose (refusing the product)	Categorical	Descriptive count (%); analyzed with multinomial mixed model with sequence and period as fixed effects
Number of empty sachets returned (adherence indicator)	Count	Descriptive count (mean ± SD), analyzed with Poisson mixed model with sequence and period as fixed effects
Report on product sharing (adherence indicator)	Categorical (binary)	Descriptive count (%); chi-square test
Number of times per day the product was consumed at home (intake frequency)	Count	Descriptive count (mean ± SD), analyzed with Poisson mixed model with sequence and period as fixed effects
Perceived liking scores (by caretakers)	Ordinal (Likert scale)	Descriptive medians (IQR), analyzed with Poisson mixed model regressions with sequence and period as fixed effects
Product ranking/selection (by mothers)	Count	Descriptive count (%); analyzed with Poisson mixed model with sequence and period as fixed effects
Food frequency changes during each product trial	Count	Descriptive means (SD); analyzed with repeated-measures LMM with sequence and period as fixed effects or non-parametric Friedman test (if not normal)
Breastfeeding frequency during each product trial	Count	Descriptive count (mean ± SD); LMM or Poisson mixed model with sequence and period as fixed effects to assess differences between treatments

Adverse effect report (diarrhea, vomiting, and any others)	Count	Descriptive incidence rates; analyzed with Poisson mixed model with sequence and period as fixed effects

Sub-study 2: Microbiome and gut health

Gut health parameters will be analyzed as both independent variables and potential mediators of treatment effects. To investigate the association between intestinal, inflammation microbiome composition and enteropathogen burden and relapse rates, relapse will be modeled using multivariable logistic regression, incorporating gut health metrics and adjusting for baseline anthropometry, age, sex, treatment group, and site. Where appropriate, longitudinal modeling will be used to examine how changes in gut health over time relate to relapse risk.

To investigate the effects of the intervention RUTFs (SMS-RUTF and S-RUTF) on gut health, we will conduct exploratory analyses of fecal microbiome composition, enteropathogen burden, and inflammation markers collected at baseline, discharge, and 3 months post-discharge. Alpha diversity (e.g., species richness, Shannon index, Simpson index) and beta diversity (e.g., Bray–Curtis dissimilarity, weighted UniFrac, Jaccard) will be assessed and modeled over time using mixed-effects models or permutational multivariate analyses (PERMANOVA), adjusting for relevant covariates and repeated measures per subject.

To identify microbial taxa differentially abundant across treatment groups and over time, we will apply one or more appropriate statistical methods that account for the compositional nature of microbiome data, sparsity, and longitudinal study design. These include recent extensions of generalized linear mixed models, log-ratio based approaches, or bias-corrected frameworks that support repeated measures. The choice of tool (e.g., ANCOM-BC, LinDA, MaAsLin, or others) and transformation (e.g., CLR, ALR, log1p) will be guided by data distribution, sparsity, and sensitivity analyses. All models will adjust for potential confounders such as age, sex, nutritional status, and site, and results will be corrected for multiple testing using false discovery rate control.

As this is an exploratory sub-study nested within a parent randomized-controlled trial, we will adopt a discovery-driven approach to refine appropriate gut health metrics and test associations with clinical outcomes such as relapse to wasting. Results from these analyses will inform future hypothesis-driven studies on microbiome-directed nutritional interventions in severe acute malnutrition.

Sub-study 3: Costing

We will have two activities in our ABC-I study, which are the treatment of MAM and the ambulatory treatment of SAM. For these activities, we will assess the cost categories listed in Table 10.

Table 10. 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 ambulatory treatment of SAM or MAM, beginning at admission and ending at discharge

Indirect costs	Costs to caregivers incurred due to receiving ambulatory SAM treatment, such as 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 the facilities. 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 gross domestic product (GDP) (36,37) and estimated amount of time spent participating in the program.
Personnel	Salaries of health workers involved in the admission, follow up, and discharge of ambulatory SAM children
Overheads	Costs of infrastructure, management, administration, and logistical support

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. Cost-efficiencies and cost-effectiveness will be calculated as the outcome definitions given in Table 3 above.

If the interventions are demonstrated to be superior for relapse or recovery outcomes, we will calculate the cost per disability adjusted life year (DALY) averted between each intervention arm and the control. To do this, we will construct a decision tree mathematical 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 (38). Both probability and deterministic sensitivity analyses will be conducted.

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