

BMJ Open Solutions to Enhance Health with Alternative Treatments (SEHAT) protocol: a double-blinded randomised controlled trial for gut microbiota-targeted treatment of severe acute malnutrition using rice bran in ready-to-use therapeutic foods in Indonesia

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ABSTRACT

Introduction Current formulations of ready-to-use therapeutic foods (RUTFs) to treat severe acute malnutrition (SAM) in children focus on nutrient density and quantity. Less attention is given to foods targeting gut microbiota metabolism and mucosal barrier functions. Heat-stabilised rice bran contains essential nutrients, prebiotics, vitamins and unique phytochemicals that have demonstrated favourable bioactivity to modulate gut microbiota composition and mucosal immunity. This study seeks to examine the impact of RUTF with rice bran on the microbiota during SAM treatment, recovery and post-treatment growth outcomes in Jember, Indonesia. Findings are expected to provide insights into rice bran as a novel food ingredient to improve SAM treatment outcomes.

Methods and analysis A total of 200 children aged 6–59 months with uncomplicated SAM (weight-for-height z-scores (WHZ) <−3, or mid-upper arm circumference (MUAC) <115 mm or having bilateral pitting oedema +/++) or approaching SAM (WHZ<−2.5) will be enrolled in a double-blinded, randomised controlled trial. Children in the active control arm will receive a locally produced RUTF; those in the intervention arm will receive the local RUTF with 5% rice bran. Children will receive daily RUTF treatment for 8 weeks and be monitored for 8 weeks of follow-up. Primary outcomes include the effectiveness of RUTF as measured by changes in weight, WHO growth z-scores, MUAC and morbidity. Secondary outcomes include modulation of the gut microbiome and dried blood spot metabolome, the percentage of children recovered at weeks 8 and 12, and malnutrition relapse at week 16. An intention-to-treat analysis will be conducted for each outcome.

Ethics and dissemination The findings of this trial will be submitted to peer-reviewed journals and will be presented

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Implementation of this double-blinded, randomised controlled trial is the most rigorous, gold-standard study design to assess the effectiveness of a rice bran based ready-to-use therapeutic food (RUTF) intervention and to limit bias.
- ⇒ The findings of the study will contribute new information on the effects of rice bran as a novel food ingredient for severe acute malnutrition treatment.
- ⇒ Sharing RUTF among household members can potentially limit the study's effectiveness.
- ⇒ Inaccurate reports of consumption by caregivers could introduce response bias.

at relevant conferences. Ethics approval obtained from the Medical and Health Research Ethical Committee at the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada Yogyakarta Ref. No.: KE/FK/0546/EC/2022 and KE/FK/0703/EC/2023 and from Colorado State University IRB#1823, OHRP FWA00000647.

Trial registration number NCT05319717.

INTRODUCTION

Severe acute malnutrition (SAM) remains a leading global contributor to early childhood morbidity and mortality and is associated with an increased risk of cognitive impairments and non-communicable and chronic diseases later in life.^{1–3}

In Indonesia, SAM remains a major public health problem affecting over 2 million children, while <1% receive adequate treatment

due to limited coverage of existing treatment options and lack of availability of ready-to-use therapeutic food (RUTF).^{4,5} The aetiology of malnutrition is complex, and there are gaps in the mechanistic understanding of the relationships between undernutrition, infections and the developing gastrointestinal microbiota. The developing intestinal microbiome may play a pivotal role in SAM pathogenesis, with SAM children experiencing an immature gut microbiota characterised by lower diversity that can persist even after malnutrition recovery.⁶⁻⁹ A causal role of the microbiome is also associated with environmental enteric dysfunction and impaired gut mucosal immunity.¹⁰

The current formulation of the standard SAM nutritional treatment globally is a RUTF¹¹ that was developed in the late 90s with the main goal of achieving rapid nutritional recovery for SAM patients. These RUTFs, however, do not take into consideration the factors of intestinal microbiome maturation, enteric dysfunction and gut mucosal immunity that involve the risk of developing non-communicable diseases later in life.^{3,12} New evidence has emerged that maternal and fetal under-nutrition increases a population's susceptibility to over-nutrition and diet-related non-communicable diseases in adolescence and adulthood,¹³ a situation of growing concern with doubling rates in Indonesia.⁴ The double burden of malnutrition (DBM) is defined by the WHO as 'the coexistence of undernutrition along with overweight and obesity, or diet-related non-communicable diseases, within individuals, households and populations, and across the life course'.¹⁴ DBM can be seen as a life-cycle problem,^{15,16} as children suffering from malnutrition in early life may have metabolic or body fat distribution profiles that predispose them to nutrition-related non-communicable diseases¹⁷ if their diets switch towards dietary patterns rich in sugary foods and oils and low in fruits and vegetables, as usually happens when a nutritional transition occurs.^{18,19}

An emerging focus exists on whole-food-derived prebiotics as a promising tool in infant health promotion and disease treatment, with long-lasting effects after administration.^{20,21} The utility of prebiotics contained within nutrient-dense foods such as rice bran is novel for SAM treatment with tremendous global health impact potential to enhance effectiveness via repairing gut dysbiosis, reducing diarrhoea and intestinal permeability, and supporting enhanced nutrient absorption.

Rice bran, a major coproduct of white rice processing, has been identified as a highly promising novel ingredient for RUTFs based on the nutritional and prebiotic composition, as well as potential affordability and accessibility in developing countries that grow rice as a staple crop.^{22,23} Rice bran is rich in fibre, phytochemicals, essential fatty acids, and amino acids and has a unique profile of vitamin E isoforms and several B vitamins.^{24,25} Rice bran supplementation has been shown to protect against enteric pathogens and diarrhoea from *Salmonella enterica*

Typhimurium,^{26,27} rotavirus²⁸ and norovirus.²⁹ Rice bran supplementation enhanced gut mucosal barrier functions via supporting the growth of native gut probiotics as part of the commensal microbiota.^{28,30} The microbial metabolism of rice bran has also been previously demonstrated in healthy infant feeding trials.^{31,32} The completed phase 1, dose-escalation clinical trials performed in Mali and Nicaragua found increased linear growth, reduced incidence of diarrhoea and improved markers of intestinal permeability in healthy weaning infants consuming rice bran daily for 6 months. These studies demonstrated favourable changes in gut microbiota composition and function with dietary rice bran supplementation and progression towards increased alpha diversity 1 month earlier than the age-matched and sex-matched control group.³³

Previous gut-microbiota-directed RUTF studies have explored the addition of prebiotic-rich ingredients such as oats, chickpea flours, green bananas, and lentils and their effectiveness in improving health outcomes in children recovering from uncomplicated SAM.³⁴⁻³⁷ However, to our knowledge, the inclusion of rice bran in the treatment of malnutrition has not yet been studied. The Solutions to Enhance Health with Alternative Treatments using rice bran study (SEHAT, or 'healthy' in Indonesian) is designed to identify changes in anthropometry and morbidity, alongside gut microbiota and dried blood spot (DBS) metabolites of children treated with a rice bran based RUTF when compared with a local RUTF that was previously tested for acceptability and effectiveness.^{38,39,40} In addition, this randomised controlled trial (RCT) will also collect skinfold measures and cognitive development assessments at multiple time points before, during and after treatment. The RCT investigation of a novel RUTF containing heat-stabilised rice bran is anticipated to deepen our understanding of gut-microbiota-targeted RUTFs that can treat malnutrition and also prevent or reduce malnutrition relapse.

Objectives

The objective of this study is to determine the effectiveness of the RUTF with rice bran compared with the RUTF without rice bran. Primary outcomes will be measured at baseline, weeks 4, 8, 12 and 16:

- ▶ Weight gain measured as g/kg/day, method of aggregation=median.
- ▶ Changes in weight-for-height z-scores (WHZ), length-for-age (LAZ), weight-for-age (WAZ), method of aggregation=median.
- ▶ Mid-upper arm circumference (MUAC) measured in mm/day, method of aggregation=median.
- ▶ Morbidity: measured as the number of days for an event occurrence (ie, diarrhoea, fever, vomiting, upper or lower respiratory infections) per child, method of aggregation=proportion and mean.

Secondary outcomes include

- Stool microbiota composition, change from baseline at weeks 4, 8 and 16.
- DBS metabolite profile, change from baseline at weeks 8 and 16.
- Percent of children recovered from acute malnutrition ($WHz \geq -2$ and/or $MUAC \geq 125$ mm) at week 8 or week 12.
- Malnutrition relapse at week 16, defined as any child recovered at week 8 or 12, and at week 16 no longer has $WHz \geq -2$, and/or $MUAC \geq 125$ mm. This analysis will be measured as a percentage.

METHODS

Trial design and study period

This study is an intention to treat (ITT), double-blinded, comparative, RCT and the protocol was designed as a collaboration between Colorado State University (CSU), USA, the Institut de Recherche pour le Développement, France, and PT Santulita Vikasa (Savica), Indonesia. The SEHAT study is funded by the Thrasher Research Fund. Enrolment began in December 2022 and the trial is expected to continue through September 2023.

Field workers in this study are recruited by Savica for data collection in the SEHAT study. Field workers are Indonesians, with a minimum education of an associate degree (D3) in Nutrition, have experience in research and fieldwork, and live in Jember or are willing to relocate for the duration of the study. These field workers will receive a thorough 2-week training course in Jember prior to beginning field work. Only field workers who pass the training assessment will be recruited for the fieldwork. All staff except the field coordinator will work directly with participants in both intervention arms and are blinded to RUTF treatment arms.

At inclusion, eligible children will be randomised to one of the two treatment arms. The participants will be individually randomised and stratified by two age groups (6–23 and 24–59 months). For each age group, the four treatment codes will be randomly distributed, using a block size of 8. Both intervention arms will follow the standard protocol defined by national SAM treatment guidelines from the Ministry of Health of Indonesia.⁴¹ Participants will receive RUTF for eight consecutive weeks and will be followed up with growth measures and biospecimens for another 8 weeks after the treatment to evaluate malnutrition relapse.

Study setting

This study will take place in Jember district, East Java province, Indonesia. The district has a population of more than 2.3 million people, distributed over 31 subdistricts. According to the Indonesian Nutrition Status Study 2021 and Basic Health Research 2018, the prevalence of wasting ($WHz < -2$) among children under 5 in Jember is 12.8%, twice the East Java average of 6.4% and the second-highest prevalence in the province.⁴² The prevalence of underweight and stunting in the district is also

higher than the East Java average, with 19.8% and 22.5%, respectively, compared with 16.1% and 15.2% prevalence in the province.

East Java is among the 13 provinces in Indonesia with the highest incidence of diarrhoea (6.6%).⁴³ Coverage of basic immunisation in Jember Regency in 2017 was 87.2%,⁴³ which is lower than the East Java average of 96.5%. Additionally, based on the Indonesian Basic Health Survey, the prevalence of malaria in East Java is very low (0.02%).⁴ In this region, agriculture remains a significant economic activity, however, urbanisation is progressing rapidly, leading to changes in diets, such as increased access to processed foods. Due to low family income, in East Java, only 58% of the population can afford a nutritious diet.⁴⁴

Site selection and eligibility criteria

The initial data on SAM prevalence per subdistrict were provided by the Jember District Health Office. The fifteen subdistricts with the highest prevalence of SAM were initially selected. The intervention area was then expanded to include a total of 19 subdistricts that had high SAM prevalence.

Standardised anthropometry measurements of weight, height, MUAC and oedema assessments will be conducted. Weight and height will be calculated as a Z-score for WAZ, height-for-age and WHz using WHO growth standards.⁴⁵ Eligible participants are children aged 6–59 months who are approaching SAM ($WHz < -2.5$) or have SAM ($WHz < -3.0$ and/or $MUAC < 115$ mm) or have bilateral pitting oedema +/++. Field workers will then assess the exclusion criteria as detailed in table 1. If the child has no exclusion criteria, they will receive a health check from the study team's medical doctor. The medical doctor will assess the child using the Integrated Management of Childhood Illness⁴⁶ form and determine the diagnosis. Children who meet one or more exclusion criteria, or if the caregiver does not consent to participate, will be referred to the health centre for further treatment. If the child is referred to the health centre for treatment of an illness, after finishing any relevant medication, they will be checked again for study eligibility by the medical doctor. During the medical check-up, if the child meets all the inclusion criteria, the doctor will collect the first DBS and measure haemoglobin concentration using a Hemocue device. If the child suffers from severe anaemia ($Hb < 70$ g/L) she/he will be withdrawn from the study and referred to the local health centre. The doctor will also give the caretaker two stool sample tubes and information on how to fill the tubes before the enrolment/baseline visit.

Details on inclusion, exclusion and withdrawal criteria can be found in table 1.

Interventions

The trial will have two intervention arms:

1. One hundred children receiving local RUTF.

**Table 1** SEHAT SAM children eligibility screening, enrolment and treatment allocation

Study phase	Inclusion criteria	Exclusion criteria	Withdrawal criteria
Screening	Age 6–59 months Parental consent for screening including willingness to provide blood and stool samples for the study Being identified as approaching SAM (WHZ<−2.5), or SAM (WHZ<−3.0 or MUAC<115 mm, or having bilateral pitting oedema +++) Being qualified for outpatient treatment Not having consumed RUTF in the last 2 months	Body weight <4.0 kg Being diagnosed with severe anaemia (Hb<70 g/L) Participating in another clinical trial SAM with complications requiring hospital treatment* Having known allergies to one of the nutritional treatment ingredients Being a sibling of an enrolled child Being a twin Plan to move out of the region during the 4 months Having Tuberculosis (TB), HIV or systemic infection Clear congenital disorder that interferes with normal nutrient intake	
Enrolment	Sign the study enrolment informed consent Pass appetite test	Being detected with medical complications, with TB, HIV positive status, one or more IMCI signs, severe oedema (+++) Having any congenital disorder that interferes with normal nutrient intake; chronic conditions including but not exclusively disorders of heart, kidney or liver Failed appetite test	
Postallocation			Not consuming RUTF at all in >4 days a week in two consecutive weeks Not providing biological stool or DBS samples Not completing forms/questionnaires at study visits Developing medical complications requiring hospitalisation Not gaining weight† after 4 weeks of treatment Developing major reactions to the intervention The caregiver wishes to withdraw their child from the study

*On discharge from hospital, the child will be re-evaluated for inclusion in the study.

†Considered as having same or less weight as baseline measurement.

Hb, haemoglobin; IMCI, Integrated Management of Childhood Illness; MUAC, mid-upper arm circumference; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; SEHAT, Solutions to Enhance Health with Alternative Treatments; WHZ, weight-for-height z-scores.

2. One hundred children receiving local RUTF-Rice Bran.

Both intervention groups will follow the standard protocol defined by national guidelines per programme

admission and exit criteria.⁴¹ This includes treatment with Amoxicillin at enrolment, given by the field team. Vitamin A will be given by the health centre, and deworming will only be completed by the field team if

Table 2 RUTF ingredient and nutritional profile

	RUTF-rice bran	RUTF
Ingredients, g/100g		
Palm oil	20.8	21.7
Whole milk powder	18.1	17.6
Peanut butter	8.6	8.6
Sugar	14.4	15.0
Whey protein concentrate	8.0	7.9
Skim milk powder	4.0	6.7
Wheat flour	8.7	9.2
Rice flour	8.4	8.7
Maltodextrin	0.1	0.7
Vitamin and minerals premix	2.0	2.0
Rice bran	5.0	–
Cocoa powder/vanilla	1.4	1.4
Proprietary ingredients (binder)	0.5	0.5
Nutrient composition, g/100g		
Energy, kcal/100g	520	534
Protein	15.0	13.5
Fat	31.1	31.6
Carbohydrate	44.4	49.0
Fibre	2.0	1.5
Protein-energy ratio	11.5	10.1
Fat-energy ratio	53.8	53.2
RUTF, ready-to-use therapeutic food.		

the child has not yet received this treatment. The two different RUTFs will be provided in single-use packages, assuring 500Kcal intake per sachet. The dose will depend on the child's weight at baseline, and it will be adjusted according to the child's weight, which will be measured weekly during the course of the treatment.

Ready-to-use therapeutic foods

The control RUTFs and experimental rice bran RUTFs are produced locally by the South East Asia Food and Agricultural Science and Technology Centre and the Department of Community Nutrition, Bogor Agricultural University in Bogor, Indonesia and transported in batches to study sites in Jember. The locally produced RUTF for this RCT is based on the results of a previous study³⁸. Both RUTFs are from the same source and similar recipes that consist of a wafer filled with a paste containing palm oil, whole milk powder, peanut butter, sugar, whey protein concentrate, skim milk powder, wheat flour, rice flour, premix of vitamin and mineral, maltodextrin and vanilla/cocoa powder (table 2). The difference between the RUTFs is that in the case of the RUTF with rice bran, the maltodextrin content was decreased, along with small modifications

in skim milk powder, oil, sugar and wheat flour, and replaced by 5% rice bran. The heat-stabilised rice bran is supplied by CSU (purchased from Stabil Nutrition, formerly Rice Bran Technologies, California, USA). The safety of the locally produced RUTFs has been assured by following the international standards developed by WHO on the maximum toxin levels allowed,¹¹ and by complying with the Recommended International Code of Hygienic Practice for Foods for Infants and Children of the Codex Alimentarius Standard CAC/RCP 21-197. The products are produced in a facility that is GMP and Halal certified by Indonesian regulating bodies, and passed microbiological and chemical food safety standards before being distributed, as confirmed by product manufacturers PT Javaindo Maju Sejahtera, Depok, Indonesia.

Study procedures

Screening

Participants will be identified through screening from health centres' e-PPGBM (elektronik Pencatatan dan Pelaporan Gizi Berbasis Masyarakat) nutritional status database. Data from e-PPGBM will be validated with the most updated data from community health workers in the respective health centre capture areas. Children with moderate and severe wasting and those with growth faltering or severe underweight will be invited to a screening at the nearest health post or visited in their homes. After parental consent for screening, they will be checked for the initial eligibility criteria.

Enrolment/baseline

Children who pass all eligibility criteria after screening and the medical exam will be given a unique identification number and randomly assigned to one intervention group. After study enrolment informed consent, they will be invited to the appetite test within the same week of the medical examination. The appetite test will be done at the child's home using a sachet of the product previously assigned through randomisation. The caregiver will give the product to the child, and after 30 min, the remaining product will be collected and weighed by the fieldworker to determine the amount consumed. The criteria to pass the appetite test according to the Ministry of Health Guidelines on the Treatment of SAM⁴¹ are shown in table 3 and depend on the child's weight. If consumption is low but the caregiver demonstrates motivation to help the child eat, the child may be left with the product to consume in the proceeding 24 hours. After 24 hours the remaining product will again be collected and weighed by the fieldworker to determine the amount consumed. If the child fails the appetite test, she/he will not be enrolled in the study and will be referred to the health centre.

Enrolment into the study will be confirmed if the caregiver's informed consent has been obtained and after a child passes all eligibility criteria, and the appetite test.

After enrolment, fieldworkers will conduct anthropometry measurements (weight, height, MUAC, oedema and

**Table 3** Criteria to pass appetite test

SAM child's weight (kg)	No of RUTF rolls consumed*	Proportion of sachet of RUTF consumed during the appetite test†
4–6.9	1.75 rolls	1/4
7–9.9	2.25 rolls	1/3
10–14.9	3.5 rolls	1/2

*According to Ministry of Health Guidelines.³⁶

†One sachet of RUTF contains seven rolls.

RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition.

skinfold thickness), and collect stool samples. Weight will be recorded to the nearest 0.1 kg on SECA scales (Seca 874 Flat Scales, Seca 874DR flat scales) and measurements will be carried out two times. The measurement is repeated for the third time if there is a difference in the results of the first and second measurements of more than 0.2 kg. Length and height will be recorded to the nearest 0.1 cm using ShorrBoard. Length in the supine position will be taken in children younger than 24 months, while older children will be measured standing. Children measuring less than 87 cm will also be measured in a supine position even if older than 24 months of age. All measurements are to be taken twice and if the difference between measurements 1 and 2 is >0.2 cm, height measures will be repeated and the third or fourth measurement will be recorded. MUAC will be measured on the left arm with a standard MUAC tape. Measurements will be recorded to the nearest 0.1 mm and carried out two times. Measurements will be repeated for the third time when there is a difference in the results of the first and second measurements of more than 0.2 cm. The presence of oedema will be determined by a visible shallow imprint after pressing both feet for 3 seconds. The presence of oedema grade 1 (bilateral pitting oedema on feet) or grade 2 (bilateral pitting oedema on feet and lower legs and/or hands/ lower arms) is considered uncomplicated SAM. Skinfold thickness will be measured using The Lange skinfold callipers at four points: triceps, biceps, subscapular and suprailiac. Measurements will be carried out twice and if the results of the examination differ by more than 2 mm then a third measurement will be carried out.

The following day the fieldworker will interview the caretaker at home and fill out the baseline questionnaire, food security questionnaire and dietary data, which includes a 24-hour dietary recall, and infant and young child feeding (IYCF).⁴⁷ The 24-hour food recall will be collected using open-ended questions related to the child's consumption in the last 24 hours. All foods and drinks consumed and amounts will be recorded on paper by the field worker. This is followed by the IYCF questionnaire on the tablet which uses an age-specific scoring system to assign points based on particular feeding practices. Developmental milestones will also be collected based on the child's age using the Caregiver-Reported

Table 4 RUTF consumption dose according to children's body weight for SEHAT RCT

Child's weight (kg)	Sachet per day	Sachet per week	Kcal per day
4.0–4.9	1 1/2	10	750
5.0–6.9	2	15	1000
7.0–9.9	3	20	1500
10.0–14.9	4	30	2000

RCT, randomised controlled trial; RUTF, ready-to-use therapeutic food; SEHAT, Solutions to Enhance Health with Alternative Treatments.

Early Development Instruments (CREDI).⁴⁸ This open-source tool asks for recollection by the caretaker of their child's age-related capabilities and behaviours.

Age will be calculated from either the birth certificate or, if not available, from their personal Maternal and Child Health Handbook, government-issued books where the child's growth and development are recorded, starting with antenatal care visits. Birthweight and birth delivery mode will be collected through maternal reports or the Maternal and Child Health Handbook.

At the baseline visit, the fieldworkers will provide information to caregivers on how to give the RUTF to the child and provide a 1-week supply of RUTF based on the child's body weight (table 4) according to WHO standards.⁴⁹ RUTF will be delivered to households weekly by field workers. Caregivers will be asked to keep the unconsumed products and the empty sachets and trained to record daily consumption in a monitoring book provided by the field team. If the caregiver is unable to read and write, a family member or neighbour will be asked to assist.

Weekly visits

Monitoring will be conducted weekly for eight consecutive weeks of RUTF intervention. During the weekly home visits, the fieldworker teams will conduct anthropometric measurements for weight, and MUAC, as well as record any oedema, any side effects from the RUTF (rash, vomiting, diarrhoea), and check morbidity through a recall questionnaire (table 5). Fieldworkers will collect caregiver diaries of the amount of RUTF consumed each day of the corresponding week and the remaining sachets. The packages of RUTF consumed and the remaining sachets will be transported back to basecamps. At the basecamps, field workers will weigh the leftover unconsumed RUTF to calculate and record weekly consumption. At the end of week 4, fieldworkers will also measure height and skinfold thickness and collect stool samples.

For those who withdraw from the study during the RUTF intervention, an exit home visit will be conducted by field workers.

At week 8, RUTF treatment will end for all participants. At this visit, in addition to weekly anthropometric measures, fieldworkers will also measure height and skinfold thickness, collect stool and DBS samples, as well as

Table 5 Schedule of enrolment, interventions and assessments, SEHAT Indonesia

Time point	Screening	Enrolment/ baseline		Postallocation		Follow-up		
		Weeks 1–3	Week 4	Weeks 5–7	Week 8	Week 12	Week 16 or exit*	
Enrolment								
Eligibility screen	X							
Exclusion criteria	X							
Medical exam/IMCI	X							
Appetite test		X						
Informed consent	X	X						
Allocation		X						
Interventions								
RUTF- rice bran				↔				
RUTF				↔				
Assessments								
MUAC (mm)	X	X	X	X	X	X	X	X
Weight (kg)†	X	X	X	X	X	X	X	X
Height/length (cm)	X	X		X		X	X	X
Oedema (+/++/++)	X	X		X		X	X	X
Baseline questionnaire		X						
Assessment of feeding practices (24 hours recall and IYCF module)		X				X		X
Food security assessment		X						
Morbidity monitoring	X		X	X	X	X	X	X
Side effects monitoring			X	X	X			
Intake monitoring			X	X	X			
Stool sample		X		X		X		X
Blood spot sample	X					X		X
Hb level (g/L)‡	X					X		X
Skinfold measurements§ (mm)		X		X		X	X	X
Developmental milestones¶		X				X		X
Reason for drop out/exit*								X

*Exit data will be collected only for children who withdraw from the study during the RUTF intervention.

†Taken with SECA scales.

‡Taken with HemocueHb201⁺.

§Taken with Lange Skinfold Callipers, factory calibrated to an accuracy of ± 1 mm.

¶Caregiver-Reported Early Development Instruments, Harvard Graduate School of Education.

Hb, haemoglobin; IMCI, Integrated Management of Childhood Illness; IYCF, infant and young children feeding; MUAC, mid-upper arm circumference; RUTF, ready-to-use therapeutic food; SEHAT, Solutions to Enhance Health with Alternative Treatments.

measure haemoglobin levels. The IYCF, 24-hour dietary recall and developmental milestones will also be collected.

Follow-up

A follow-up visit will be conducted at week 12, during which weight, height, MUAC, oedema and skinfold thickness measurements will be performed. Information on morbidity will also be collected. The study will end at week 16 for all participants. At this final visit, weight, height, MUAC, oedema and skinfold thickness measurements will be collected as well as DBS, haemoglobin and

stool samples. Morbidity, IYCF, 24-hour dietary recall and developmental milestones will also be recorded.

Sample size

We aim to recruit 100 children per group (or 200 children in total) to ensure sufficient statistical power. If the Indonesian RUTFs meet the WHO requirement for an average increase in weight gain of 5 g/kg BW/day,^{46 49} a total sample size of 112 children (56 per group) would allow the detection of a 20% difference between control and intervention arms. This

calculation considers an SD of 1.5 g/kg BW, a significance of 0.05 and a power of 0.80. If 15% of children drop out during the intervention, a total sample size of 132 children would be required (66 children per group). If children fail to reach this 5 g/kg BW target and only gain 2 g/kg BW/day, the previous study on the efficacy of this locally produced RUTF that was assessed in Bogor, Jakarta, Indonesia will be used as reference.³⁸ This study calculated a sample size of 75 children per group which allowed for detection of a 30% difference between the control product and the local product. Furthermore, additional power calculations for secondary outcomes returned lower numbers of required children per group.³³

Randomisation and blinding

A total of 200 children will be randomly allocated to either intervention group, using a computer-generated randomisation list with a block size of 8, and two different codes per treatment group, for a total of four codes. Randomisation will occur by children's age group (6–23 months and 24–59 months) within each treatment group. Randomisation will be done by one of the principal investigators (PI), who will not interface with participants to avoid interference with study blinding. Researchers, caregivers and field teams will be blinded to the intervention until completion of the study. Only two PIs, who will not be in the field, will know product allocation. All products will be packaged the same in aluminium foil and labelled by a code and product flavour.

Data collection and management

All study participants will be assigned a study identification number. Data to be collected include demographic data (living conditions, ethnicity, sex, caregiver age/education, food security), morbidity, anthropometry (weight, height, MUAC, oedema, skinfolds), dietary data (breast feeding, food frequency and dietary diversity), birth weight and method. Cognitive development using CREDI will also be monitored and recorded. Biospecimens (stool and DBS via finger prick) will be collected from the participants, labelled with the participant ID number and study visit number, and frozen at -20°C in freezers at the basecamps. All DBS cards will be shipped to CSU for metabolite analysis. Two stool samples will be collected from participants at each respective time point, and one sample will be shipped to CSU for faecal microbiome analysis. The second stool sample will remain in Indonesia at Bogor Agricultural University for future use.

During screening and baseline visits, data will be recorded on paper by fieldworkers, and input into the KoboToolbox application on an offline tablet. On return to basecamps, all data input will be monitored and verified by the field supervisors and uploaded to the KoboToolbox online cloud. Paper documents from children not enrolled in the study will be destroyed, while the others will be stored in the Savica main office. KoboToolbox is a data collection, management and visualisation

platform ensuring frequent system backups are stored in encrypted locations. All data are accessible only behind password-protected accounts, and only primary investigators and designated study members will have access to data via user-specific login with a password. All metadata will be checked regularly and downloaded from KoboToolbox as an Excel file. The downloaded metadata file will exclude participant identifiers and use only study participant ID numbers. This metadata file will be used to relate anthropometric, morbidity and demographic outcomes to microbiome and metabolomic data. At no time will the names of individuals be reported nor associated with samples. There are no additional data available at this time.

Data analysis

A mixed model to capture repeated measures will be employed to measure primary outcomes. Fixed effects include treatment (RUTF, RUTF-Rice Bran), time (baseline, weeks 4, 8, 12 and 16), sex and age, and interactions. Child ID will be used as a random effect to capture correlated responses on the same child. Physiological clinical primary outcomes, including body composition, weight gain, anthropometric indices and morbidity, will be assessed between the two intervention arms. The number of missing data will be given for each variable and missing data will not be imputed on primary outcomes. All endpoints will be analysed on the ITT population.

Secondary outcome analysis of biospecimens from each time point will be performed to elucidate changes in microbiota and metabolites intraindividually over time and between treatment arms at each time point. Infant stool microbiota composition will be assessed using 16S rRNA amplicon sequencing and shotgun metagenomic sequencing. DBS will undergo non-targeted metabolite analysis via ultra-high-performance liquid chromatography-tandem mass-spectrometry (UPLC-MS/MS).

Ethics and dissemination

Ethical approvals

The study protocol details as described in this manuscript and all study forms have Colorado State University IRB approval (IRB #1823, OHRP FWA00000647), and approval through the Medical and Health Research Ethical Committee (MHREC) at the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada in Yogyakarta, Indonesia Ref. No.: KE/FK/0546/EC/2022 and KE/FK/0703/EC/2023. Any modifications to the study protocol that may affect the conduct of the study will be discussed as a team and presented for approval to the ethical review boards. SEHAT study's results will be disseminated through peer-reviewed relevant journals, and abstracts will be presented at relevant national and international conferences.

Safety

Prior to the fieldwork, the PIs and researchers will train the field team on research ethics, guidelines, and data collection tools, practice in anthropometric measurements, blood and stool sampling, appetite test and familiarisation with computer tablets and digitalised study tools. A field simulation will be conducted at the end of the training. The field team and the representatives of the selected health centres will also receive training on the Indonesian national guidelines for Integrated Management of Acute Malnutrition.

Overall, the study design has minimal risks associated with the dietary intervention.

Data on adverse events will be assessed and collected weekly through a recall questionnaire at any visit or as soon as reported by children's guardians. Intervention for the child will stop for significant reactions. Adverse events will be communicated to PIs and health centre staff and include having diarrhoea (loose or watery stool more than three times in a day), presenting blood in the stool, vomiting, having fever or signs of possible allergies such as cutaneous rashes, any hospitalisation and death events. PIs also will have the final decision to terminate the trial.

Consent and patient involvement

Patients and their families will not be involved in the design, conduct or dissemination of the research. Families were involved in reporting baseline demographic data. Written informed consent will be obtained from each eligible child's parents (both mother and father) or legal guardian. Children's guardians will be told that participation in the study is voluntary, can be withdrawn at any time, and does not affect their (or family members) ability to access medical care from public health clinics. Consent by the parents/guardians/caretakers will be obtained before any study procedures. This study consists of two informed consent forms: one for the screening and one for study enrolment which will be obtained by the screening and monitoring field teams, respectively. The screening informed consent includes consent for screening anthropometric measurements, an interview of exclusion-inclusion criteria and a doctor's examination including obtaining a DBS sample, Hb examination and providing a stool sample. The study enrolment informed consent includes consent for the appetite test, all data collections from baseline, weeks 1–8, 12, 16, the 8-week RUTF intervention and documentation. This consent form agrees to the dissemination of collected data and biological specimens, that is, stool and DBS, with the partner universities participating in the study. A subsection of this enrolment consent form also asks for consent to photo and video documentation, with the child's name not being associated with the photo/video (online supplemental material 1). Fingerprints will be used as a substitute for signatures for participants who cannot provide signatures. Informed consent forms will be requested to be signed by both parents (father and mother) with the

aim that with the father's involvement the dropout rate will be minimised. The procedures and informed consent forms are approved by the ethics committees. All information will be provided in Indonesian. All hardcopy signed consent forms will be stored behind locked doors at the field basecamps. After study completion, these documents will be securely stored at Savica's office in Jakarta, Indonesia and destroyed after 5 years.

DISCUSSION

This study aims to determine the effectiveness of a RUTF with rice bran compared with a RUTF without rice bran in the community setting treatment of uncomplicated SAM. The study's strengths lie in its chosen design, which is the RCT, a gold-standard study design that reduces bias and assesses the effectiveness of the rice bran-based RUTF intervention. However, there may be potential bias related to intrahousehold product sharing and inaccurate reports of consumption by caregivers, which the team will closely monitor and support to maintain accuracy. The study's findings are expected to elucidate novel functional pathways for rice bran as a nutrient-dense source of prebiotics, phytochemicals, amino acids, vitamins, and fatty acids to improve SAM treatment.^{22 23 24}

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Contributors EPR, FTW and DDS designed the study protocol, PEG, RR and ZN formulated the study RUTFs, AMW and SB wrote the manuscript, AR and RZ provided input in the study protocol. FKP serves as field coordinator for protocol adherence and execution. EPR, FTW, DDS, PEG, RZ, AR, MDF, FKP, MCP and MvdH



revised the manuscript critically, gave final approval and are accountable for all aspects of the work.

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