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Cereals and pulse based Ready-to-Use Therapeutic Food as an alternative to the standard milk and peanut paste based formulation for the treatment of severe acute malnutrition: non-inferiority individually randomized controlled efficacy clinical trial

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Title page

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Running Head:

Efficacy of no-milk Ready-To-Use Therapeutic Food

Abbreviations:

SAM, Severe Acute Malnutrition; CMAM, Community-based management of SAM; RUTF, Ready-to Use Therapeutic Food; P-RUTF, Peanut based RUTF; SMS-RUTF, Soya, Maize and Sorghum RUTF; DDT, Deuterium Dilution Technique; TBW, Total Body Water; FM, body fat mass; FFM, Fat Free Mass; BIA, Bioelectrical Impedance Analysis; HZ, Health Zone; HC, Health Centre; MUAC, Mid Upper Arm Circumference; HIV, Human Immunodeficiency Virus; PA, phytic acid; PUFA, polyunsaturated fatty acid; %BF, Body

Fat Percentage; FMI, Fat Mass Index; FFMI, Fat Free Mass Index; P**h**A, Phase Angle; IM, Illness Marker; SD, standard deviations; IQR, interquartile ranges; 95%CI, 95% Confidence intervals; **LOS, length of stay;** ITT, Intention-To-Treat; PP, Per-Protocol

Trial registration:

The study was registered in Pan African Clinical Trial Registry (PACTR201303000475166).

Key words: severe acute malnutrition, efficacy, ready-to-use Therapeutic food, amino acid, body composition, bio-impedance analysis, deuterium oxide, hemoglobin, cereals, pulses, milk.

Abstract

Background: The cost of current standard Ready-to-Use Therapeutic Food (RUTF) is among major obstacles to the scale up of Community-based Management of Acute Malnutrition (CMAM), an important child survival strategy. Identifying a cheaper alternative is a global public health priority.

Objective: We compare the efficacy of Soya-Maize-Sorghum RUTF (SMS-RUTF) with that of standard RUTF (P-RUTF).

Design: This was a non-blinded, parallel group, simple randomised, controlled trial that enrolled two groups of SAM children (6 and 23 months and 24 – 59 months) and used a day care approach.

Results: Intention-to-treat (ITT) and per protocol (PP) analyses showed non-inferiority of SMS-RUTF compared to P-RUTF for recovery rate [Δ =-2.0%(95%CI -7.6, 3.6) in ITT and -1.9%(95%CI -5.3, 1.4) in PP], weight gain [Δ=-0.7gkg^{-1}day^{-1} (95%CI -1.3, 0.0)] and Length of stay [Δ=2.0(95% CI, −1.7, 5.8)days] in children ≥24months. In children ≤23 months, recovery rate with SMS-RUTF was inferior to that with P-RUTF [Δ=-20.8% (95%CI -29.9, -11.7) in ITT and -17.2%(95%CI −25.6, -8.7) in PP]. Treatment with SMS-RUTF resulted in a greater increase in hemoglobin [0.670(0.420, 0.921)g dl-1; p<0.001]. Treatment with both RUTFs resulted in the replenishment of all the amino acids tested, except for methionine. There were no differences at discharge between RUTF groups in fat mass [Δ=0.3(95%CI −0.6, 1.6) kg; p=0.341] of fat mass index [Δ=0.4(95%CI −0.3, 1.1) kg m^{-2}; p=0.262]. By contrast, comparisons of fat free mass indicated lower levels of FFM than the community controls after treatment with either of the two RUTFs [Δ=-1.3(95%CI −2.4, -0.1)kg; p=0.034 for comparison between community controls and the SMS-RUTF group and Δ=-1.8(95%CI −2.9, -0.6)kg; p=0.003 for comparison between community controls and the P-RUTF group].

Conclusion: SMS-RUTF can be used to treat SAM in children ≥24 months of age to reduce the costs of CMAM programmes. More research is required to optimize SMS-RUTF for younger children.

Introduction

Severe Acute Malnutrition (SAM) affects approximately 19 million children under the age of 5 and is associated with over half million preventable child deaths each year(1). This figure does not include the edematous form of SAM. Previous figures including all the forms of SAM have suggested much higher burden (2). In most developing countries, Case Fatality Rates in hospitals treating SAM remain at 20-30% and few of those requiring care actually access treatment (2). Community-based management of SAM (CMAM) has been developed to offer a new approach to delivering care to acutely malnourished children in emergency situations and in more stable settings. The model is rooted in public health principles of coverage and access and is designed to achieve population-wide impact (3). It focuses primarily on treatment of the majority of the acutely malnourished people as outpatients in their homes rather than in Therapeutic Feeding Centers (3). Intensive inpatient care is also provided for those who have complications(3). Techniques of community mobilization are used to engage the affected population and achieve high proportion of early presentation while maximizing coverage(3). A study conducted in Malawi on SAM children treated using Ready-to Use Therapeutic Food (RUTF) have also demonstrated that the majority (over 85%) of children discharged as recovered after treated using the CMAM approach maintained a normal weight for height for as long as 15 months after discharge (4).

RUTF, a lipid-based paste that is energy dense, resists bacterial contamination, and requires no cooking(5), is a central element of CMAM programs. The production of RUTF requires grinding all ingredients to a particle size of < 200 microns and embedding the protein and carbohydrate components into a lipid matrix(5). The production process avoids the introduction of water and the resultant low water activity in the product is critical to RUTF's resistance towards bacterial contamination. This in turn allow RUTF to be safely store at

ambient temperatures and used in poor communities (5). The most widely used RUTF referred as P-RUTF in this paper, is a mixture of milk powder, sugar, vegetable oil, peanut butter, vitamins, and minerals(5;6). It is equivalent to the WHO F-100 milk(7). This RUTF recipe has been used widely in CMAM to treat severely malnourished children in resource-poor settings(8) with demonstrably high recovery rates, low case-fatalities, and greater weight gain has been demonstrated using P-RUTF(2;9;10). However, the high milk content of this formulation makes it very expensive for sustainable use in resource-poor settings and increases the proportion of ingredients that have to be imported into developing countries.

To lower the cost and increase the potential for using locally grown ingredients, Valid Nutrition has developed a new milk-and peanut free recipe based on locally produced crops. This recipe is made from Soya, Maize and Sorghum (SMS-RUTF), and may provide a cheaper alternative to the P-RUTF currently used. However, the efficacy of this formulation compared to P-RUTF has not been formally demonstrated. An initial study assessing the effectiveness of SMS-RUTF in Lusaka yielded inconclusive results with the recovery rates in both the intervention and the standard group below international SPHERE standard and an unexplained high level of mortality(11). Likely explanations of the inconclusive results included the cholera and measles epidemics and floods that occurred during the study period causing abnormal increases in mortality and default rates(11). Despite these inconclusive results, lessons learned from that trial have been used to improve both the composition of the SMS-RUTF and the design of studies used to evaluate it.

The study reported here examined the efficacy of SMS-RUTF compared to P-RUTF using a design and context that minimized operational constraints. The SMS-RUTF product used had an enhanced phytic acid and iron and phytic acid and zinc molar ratios and improved omega-

6 amega-3 fatty acid profile ratio (11) compared to the product tested in Lusaka. The study also included a comparison of changes in hemoglobin, amino acid profile and body composition during recovery in addition to the standard outcome indicators of recovery rate, weight gain and length of stay. The hypotheses assumed are that SMS-RUTF is not inferior to P-RUTF for recovery rate, weight gain and LOS and that treatment with SMS-RUTF will be associated with higher hemoglobin increase.

Methods

Study design

Primary objectives

This was a non-blinded, parallel group, simple randomized, controlled trial to compare the efficacy of SMS-RUTF with that on P-RUTF in the treatment of SAM in two groups of children, those aged between 6 and 23 months and those aged between 24 – 59 months. The non-inferiority hypothesis was chosen because the overall aim of the research was to develop a RUTF as effective as the highly effective standard RUTF but cheaper and was assumed based on the result of a previous study into SMS-RUTF undertaken by this team in Lusaka, Zambia(11). Differences in the color and taste between the SMS-RUTF and the P-RUTF precluded blinding the study. To ensure that the research team had full control over all treatment parameters and could collect daily data on morbidity, a day care approach was used, wherein study subjects attended an outpatient treatment center for 8 hours each day to receive standardized treatment protocols. This day-care approach eliminated the risks that subjects shared or sold the RUTF and the risk that the energy and micronutrient densities of the RUTF was altered by inappropriate mixing with other food. The day care approach also helped improve the assessment of the adherence to the study protocol and accurately quantifying individual daily intakes of RUTF.

Secondary objectives

The study also compared changes in hemoglobin, the replenishment of amino stores and changes in body composition attributable to the two products. Hemoglobin was measured at admission and at discharge from the study and in a sub-sample of participants selected randomly throughout the study period. The replenishment of amino-acid stores was assessed by measuring plasma level of the free amino acids (lysine, valine, tryptophan, tyrosine,

phenylalanine, methionine and cysteine) in overnight-fasted malnourished children before starting nutrition rehabilitation, upon discharge from the study and in age / sex matched non-wasted community controls recruited from the same area as the malnourished participants. Body composition was assessed using two techniques. Deuterium Dilution Technique (DDT) was used to assess Total Body Water (TBW), Fat Free Mass (FFM) and Body Fat Mass (FM). This sub-study used the change in the concentration of deuterium in samples of saliva after an intake of a standardized oral dose of Deuterium oxide to estimate TBW and FM and FFM and derived indexes. It was conducted in a sub-sample of study subjects at discharge and compared to the levels found in age and sex matched non-wasted community controls. Bioelectrical Impedance Analysis (BIA) was used to also estimate TBW, FM, FFM, and derived indexes. Other specific BIA parameters of Reactance and Resistance (Phase angle, Wellness Marker), were also measured. These were assessed using a dual frequency portable Bodystat 1500MDD in another randomly selected sub-sample of children aged 24 - 59 months drawn from each of the treatment groups. These children were assessed at the beginning of nutrition rehabilitation, then again when their MUAC reached 12.5cm and again at exit from the study.

Setting

The study was undertaken in Miti-Murhesa Health Zone (HZ) located in the Kabare administrative zone of South Kivu province in Democratic Republic of Congo. The HZ covers an area of 525 km^2 adjacent to Lake Kivu and consists of highland plains and hills at elevations ranging between 900–1900m. It has a tropical highland climate. At the last census in 2011, it had a recorded population of 204,368 with a very high population density of 392 inhabitants per km^2. The main economic activities are subsistence agriculture and small scale trading. In 2011 the HZ had 40,000 children aged 6 to 59 months with a prevalence of SAM in these children of 2.2%(12). Breastfeeding is universal but the prevalence of exclusive

breastfeeding until 6 months is low with the average duration being 2.5 months (13;14). The diet of infant and young children has remained unchanged for decades and is poor in diary and other animal source foods(15). The HZ has 16 health centers (HCs) and 4 hospitals and before the study started was running a limited CMAM program with 3 outpatient sites for the management of uncomplicated SAM and one stabilization center for the management of SAM with complications. The geographical coverage of this program and the number of admissions were however very low and between May - August 2011 only 40 SAM children were admitted into the CMAM program out of a predicted case load of over 800. This study was implemented in 10 out the 16 HCs and used one of the hospitals as a referral center for the stabilization of SAM with complications.

Study populations

The study participants were selected from children admitted into the government run CMAM program in Miti-Murhesa HZ. The government CMAM program admitted all children aged between 6 and 59 months diagnosed with SAM (mid upper arm circumference [MUAC] <115mm or bilateral pitting edema of any degree). Length or height was measured but the related nutrition indices were not used either in decision to admit or discharge children or in in the definition of outcome. Children with MUAC < 115mm and good appetite and no medical complication and those with bilateral pitting edema assessed as + or ++ who also had good appetite and no medical complication were admitted directly into the day-care component of the study program. Those with bilateral pitting edema assessed as +++ degree or with any medical complication at enrolment were referred to the participating inpatient facility where they received inpatient care until stabilized, after which time they were admitted into the day-care study program. Children with any medical or nutritional complication during follow up were also referred to the participating inpatient facility for appropriate treatment of the complication, after which they were re-admitted into the day-care

program and remained in their original study group. Medical complications were defined using the World Health Organization's CMAM and Integrated Management of Childhood Illness (IMCI) standard definitions (2;16). Nutrition rehabilitation during inpatient followed the national guidelines and therapeutic milks F75 and F100 were used as appropriate.

Study subjects were admitted into the study at the same time as they were admitted into the day care phase of the study program. Great attention was given to avoid the admission into the study of any children who were not suffering from SAM and before inclusion in the study, all potential subjects were re-examined by senior supervisors (all of whom had over 10 years experience in the diagnosis and management of SAM) to confirm that the diagnosis of SAM was correct. The presence of edema, the most difficult to assess diagnostic criteria for SAM, was confirmed by the senior supervisor prior to enrolment into the study. Children admitted into the CMAM program for whom senior supervisors did not confirm presence of edema were excluded from the study. Children with congenital or acquired disorders affecting growth, any history of any food allergy, a history of treatment for SAM in the previous 3 months and those from visiting families were also excluded.

The community control groups for the body composition and amino acid studies were recruited from the same neighborhoods as the malnourished children included in the main study. These controls were matched for the age at enrolment (± 1 month) and the gender of the malnourished child. Technical difficulties in conducting the BIA assessments in children younger than 24 months meant that only children aged 24 - 59 months and above were eligible for inclusion in the BIA component.

Randomization

The study used simple randomization (ratio 1:1). After confirming eligibility for inclusion in the study, children were randomized by a closed envelope method to receive either SMS-RUTF or P-RUTF. A computer-generated sequentially numbered randomization list (with variable block sizes) that contained both allocations and codes for 900 children was pre-prepared by the trial statistician who was based outside the DRC. These were sent to the national study coordinator who then prepared 900 opaque, sealed, and consecutively numbered randomization envelops. A block of 20 envelopes were distributed to the enumerator team leaders at each study site who used them to allocate a "Study Group" to each subject at admission. The team involved in the assessment of the child for eligibility and in their follow up had no role in the allocation of the Study Group.

Monitoring and follow up

The study was conducted in specially built "study day care sites" erected at each of the participating health centers (HCs). After enrolment, caregivers were asked to bring the children to nearest site every day between 8am – 4pm until discharged and the mother or another family member had to stay with the child. At each site, a minimum of two HC nurses and one field nutritionist monitored the children's clinical and nutrition parameters, including checking the progress of nutritional recovery and identifying and treating any concurrent infection. At each site, two study assistant nurses fed the children with the support of the caregivers. Children were not allowed to take RUTF home and caregivers were advised not to feed children in the morning before coming to the site, except for children still on breast milk. No special recommendation was given for evening meal. Each study nurse assistant had less than 10 children to feed. The study nurse assistants were allocated to one study group for half of the study period before being changed to the other study group for the other half of the study.

Treatment protocol

The nutrition and medical management of children in both study groups were similar and in general followed the DRC national guidelines with the exception of the following differences: The study used an admission criteria of MUAC<115mm or bilateral pitting edema in place of the national criteria of MUAC<110mm or bilateral pitting edema; the study used a discharge criteria of MUAC≥125mm and no edema for 15 consecutive days in place of the national criteria of MUAC ≥115mm and weight gain of 20% and no edema; children in the study were followed up daily at day care centers instead of weekly at the HC in the national guidelines and the study therapeutic food was given ad libitum instead of the fixed amount of 200 kcal/kg/day in the national protocol (17).

After admission into the study, all children received a 5-day course of amoxicillin and a single 500 mg dose of mebendazole. All medications were directly administered to the child by the nurse at the day care sites in order to ensure that they were taken by the child. Vitamin A was not given because all the children had received a high dose of vitamin A of 200,000 IU within 3 months of admission and because both RUTF contained substantial amount of vitamin A (**table 1**). For any episodes of infectious disease that occurred during follow up, any treatment prescribed was also directly administered by the nurses at the day-care site.

Data collection and follow-up

The study used a combination of specially trained study nurses as supervisors and study assistant nurses and nurses from participating health facilities as enumerators. Two weeks before the start of data collection, all enumerators received training on the diagnosis of SAM, its management and the follow up of cases. They were also trained on data collection using an individual monitoring card that had been developed specifically for the study. Data collected on this form included administrative details, nutrition / medical history, physical

signs of disease, laboratory results at admission and during nutrition rehabilitation, nutrition, clinical signs and type of discharge. The nurses collected the data every morning during the period of study participation. A specially designed questionnaire book was used by study assistant nurses to collect additional information including actual RUTF intake, symptoms and physical signs of diseases observed by them during their surveillance of children at the feeding site and symptoms such as bloating, flatulence, abdominal pain or diarrhea that could have been related to RUTF intake. Special forms were designed and used for the collection of specific data for BIA parameters and saliva samples for body composition assessment and blood samples for amino acid assessment.

A trial week of the implementation of all protocols and routine data collection procedures preceded the start of the study in order to ensure the standardization of data collection and iron out any initial problems.

Procedures

Weight, height or length and MUAC were measured following WHO recommended procedures (18). Hemoglobin concentrations were measured in capillary blood, obtained from the fingertip, using a portable Hemoglobinometer (HemoCue® AB, Ängelholm, Sweden). The device was calibrated on a daily basis using a HemoCue Control Cuvette. BIA parameters were determined using the manufacturer-recommended procedures for the hand-foot Bodystat 1500 MDD system (Bodystat Inc, Douglas, United Kingdom), with accompanying measurements of weight and height. BIA was measured with the child in supine position with arms and legs slightly abducted from the trunk. The measurement started after 3 to 4 minutes in that position and was done with electrodes placed at the dorsal surfaces on wrist (between second and third metacarpals) and ankle (between second and third metatarsals) with the proximal and distal electrodes placed at a minimum of 5cm apart. The

impedance was measured at the frequencies of 50 KHz. The deuterium dilution technique (DDT) was undertaken in well-hydrated children with empty bladders. Children were considered well-hydrated if they had no history of diarrhea for the past week, had no history of strenuous activity in the past 3 hours, had wet mouth and no history of recent sunken eyes and had no clinically noticeable edema. A single 3g dose of deuterium (children <10kg) or 6g (children 10 to 20 kg) was given in the morning after an overnight fast. The deuterium dose was pre-weighed on an electronic scale accurate to 0.01 g. Saliva samples were collected before the deuterium dose (baseline sample), 3 hours post ingestion (post-dose sample 1) and 4 hours post ingestion (post-dose sample 2). The children were instructed to refrain from any food or fluid for at least 30 min before the post-dose saliva samples. Saliva was collected by getting the children to chew on a ball of cotton wool to fill the ball with saliva. The saliva was then sucked up out of the ball by a syringe. A sample collection was deemed successful if at least 2ml of saliva was collected. After collection, saliva samples were stored in a cool box for not more than 6 hours before being transferred to a freezer where they were stored at –20ºC until shipment to the Nairobi based Kenya Medical Research Institute laboratory where they were also kept frozen until analysis. The deuterium enrichment in the saliva samples was measured by Fourier Transform Infared (FTIR) spectrometry(19). In the Deuterium Dilution technique, TBW was calculated using the value of the deuterium enrichment of the saliva, and the data were analyzed in association with the weight and height measured on the day of dosing. In the BIA analysis, TBW was calculated using a predictive equation developed using anthropometric data and BIA parameters collected in Ethiopian infants and children by one of the authors (20). This equation was deemed by the authors to be more appropriate than other published equations. The FFM was derived from TBW derived using published age and gender specific constants for FFM hydration(21). Human Immunodeficiency Virus (HIV) status was determined by Determine® and Unigold® using the serial approach as

recommended by the national guidelines. Plasma samples for amino acid analysis were obtained by venipuncture and collected in tubes with EDTA as an anticoagulant. The blood samples were stored immediately into Cubecooler ™ to maintain blood temperature at 4°C to prevent micro-hemolysis and degradation of amino acid by enzymes present in blood cells (22). Samples were transported within 4 hours after collection to a laboratory for centrifugation and deproteinization. The blood was centrifuged at 3000g for 15 minutes at 4°C to separate plasma (supernatant) from blood cells. For deproteinization, 100 µl of plasma were mixed with 200ul of 5% trichloro-acetic acid and the mixture was centrifuged at 10,000g for 10min at 4°C. The supernatant obtained from this second centrifugation (deproteinezed plasma) was then stored at−20°C until shipping in bulk to the Ajinomoto laboratory in Japan and was used for plasma amino acid measurement. The amino acid was measured by an L-8900 dedicated automated amino acid analyzer (Hitachi High-Technologies, Tokyo, Japan) composed of a guard column and analytical column, following standard instruction from the device manufacturer (23).

Food products used in the study

Both study RUTFs were produced in Valid Nutrition factory in Malawi, an officially recognized UNICEF RUTF supplier. The factory has been supplying the Ministry of Health in Malawi since 2005 and has produced study foods for several published studies (11;24-30). Table 1 provides the composition of the two RUTFs obtained using the US Department of Agriculture food composition database, while **table 2** compares their amino acid profiles obtained from actual laboratory analysis of the two products. The two types of RUTF were packed in similar sachets with different colored labels. Based on our experiences from the Lusaka trial, we modified the micronutrient profile of the SMS-RUTF product used in this study, using a specially formulated vitamin and mineral premixes, and used dehulled soybean

and degermed maize. The final product met the WHO 2007 recommendations for RUTF mineral and vitamin levels. To compensate for the higher phytic acid (PA) content in the SMS-RUTF and improve the PA/iron and PA/Zinc molar ratio we increased the concentration of iron, zinc in the SMS-RUTF above the WHO recommended concentrations (31;32). To improve Iron bio-availability in the SMS-RUTF we increased the Vitamin C content above the WHO recommendations. We also increased the n-3 polyunsaturated fatty acid (PUFA) content and decreased the n-6 PUFA to obtain a n-6 PUFA: n-3 PUFA ratio less than 5(33).

A pre-trial panel test demonstrated that the above changes did not affect consistency, color, odor or taste when compared to the product used in the Lusaka trial and we therefore did not re-run acceptability trial on the product. However, to ascertain and compare the acceptability of the two trial products particularly with regard to the difference in iron, lactose and non-digestible oligosaccharides content, during the efficacy trial we collected data on abdominal pain, the occurrence of diarrhea, flatulence, abdominal distension and actual daily intake (34;35).

Outcomes

The primary outcomes of interest for this study were recovery rate, average daily weight gain and average length of stay (LOS). Secondary outcomes included hemoglobin change, difference in, Fat Mass (FM), Body Fat Percentage (%BF) and Fat Mass Index (FMI), Fat Free Mass (FFM) and Fat Free Mass Index (FFMI) Phase Angle (PhA), and Illness Marker [IM]. The Plasma concentrations of 8 key amino acids at discharge were also studied.

Sample size

We calculated the sample size to demonstrate that SMS-RUTF was not inferior to P-RUTF for recovery rate, weight gain and LOS among children with SAM discharged as recovered

from the study. The sample sizes were calculated for a power of 80% and a level of statistical significance of 0.05. The margins of non-inferiority were 10% for recovery rate, 1.2 g kg^{-1} day^{-1} for weight gain, and 14 days for LOS. These margins were defined based on the findings of our previous study conducted in Lusaka (11). For the recovery rate, the margin of non-inferiority of 10% is fixed based the Lusaka SMS-RUTF study that suggested a recovery rate of over 80% for the standard treatment (per protocol analysis) and the SPHERE standard requirement of minimum recovery of 75%. Based on data of the SMS-RUTF Lusaka study in which the weight gain rate and the 95% CI for the P-RUTF was 3.3 (2.8-3.7), the margin of non-inferiority was fixed at 1.2g/kg/day. The non-inferiority margin for the length of stay of 14 days was fixed based on the cost of the program and the fact that follow ups of these children are either weekly or fortnightly. We estimated that a difference of 14 days will be associated with a significant increase in cost of treatment in a context of restricted budget. As the findings of our earlier study in Lusaka indicated potentially different responses between younger and older children, sample sizes were calculated separately for children 6-23 months of age and for those aged 24 - 59 months (11). The sample size was calculated using the web-based software “Power”(36). A total of 448 SAM children aged 6-24 months and 316 SAM children 24 to 59 months were required to be 80% sure that the lower limit of a one-sided 95% confidence interval (CI) would be above the set limits of non-inferiority (37;38). Due to budgetary constraints convenience samples were chosen for the secondary objectives. These were 200 SAM children (100 per study group) and 20 age and sex matched community-controls for hemoglobin; 60 SAM children (30 per study group) and 60 age and sex matched community-controls for body composition by DDT; 200 SAM children (100 per study group) for body composition using BIA and 60 SAM children and 25 age and sex matched controls for the determination of the distribution of free amino acids concentrations.

Data management, definitions and analysis

Data management

Throughout the study, the data quality manager and the principal investigator conducted field supervisions during which they spot-checked the quality of anthropometric measurements, edema diagnosis, individual data collection forms and the study questionnaire books filling. All the individual data collection forms were checked again for accuracy and completeness at the time of child discharge from the study. The verified forms were then collected for data entry. Data were double entered by two enumerators into a customized Epidata database prepared for this study (39). Quality of data entry was monitored by the supervisors who cross-checked a random selection of 10% the records. Given that independent teams regularly verified anthropometry measurements, no value was excluded. Cleaned data were exported to stata-11 (40) for analysis.

Definitions

Recovery rates were defined as the percentage of children who were discharged as recovered from the study divided by the total number of children who exited the study. The total of children who exited the study included all those who defaulted, died or were discharged as non-recovered after either meeting the non-recovered criteria (90 days in the program) or at the closure of the program. A child was considered to have defaulted if he/she was absent for five consecutive daily visits and if he/she refused to return after two community workers home visits.

Rates of weight gain were calculated by dividing the weight gain expressed in grams (weight at exit –weight at admission) by the weight at admission (in kilograms) and the LOS (in days).

Average weight gains were measured as the mean of the individual weight gains expressed in g/kg/day. The average LOS was calculated by dividing the sum of individuals LOS by the total number of children included in the numerator calculation.

The hemoglobin change was the difference in blood hemoglobin concentrations between admission and discharge from the study in all children with measurements taken at both points.

FM in both the Deuterium Dilution Technique and BIA was calculated as the difference between body weight (BW) and FFM. %BF was obtained by the equation %BF=(FM*100)/BW. The FFMI (fat-free mass/height^2) and FMI (fat mass/height^2) were obtained by dividing FFM and FM expressed in kilograms, by the square of the height expressed in meters. Resistance (R) and reactance (Xc) were adjusted for height by dividing the observed values of these BIA parameters by the height of the child (41). PhA and IM were calculated directly by the BIA Bodystat MDD machine.

Analysis

Means and standard deviations (SD), medians and interquartile ranges (IQR) or proportions and 95% Confidence intervals (95%CI) were used to describe the admission and exit parameters, as appropriate. Means were compared using t-test, medians using the Mantel–Haenszel test and proportions using the Student's chi-squared test. Differences in the estimated marginal mean between the treatment groups along with a bootstrapped 95% CI was estimated to draw inference on non-inferiority.

For the primary outcomes, in accordance with recommendations for analyzing and reporting equivalence and non-inferiority studies, both Intention-To-Treat (ITT) and Per-Protocol (PP) analyses were performed and the confidence intervals were used to interpret any differences (42;43). The ITT analyses included all children enrolled in the study. The PP analyses for recovery rates included all children discharged out of the program as recovered, dead or non-

recovered but excluded children who defaulted or who transferred out of the program and were lost to follow-up after inpatient transfer. The PP analyses for weight gains included only the children who were discharged as recovered. Logistic regression was used to test for interactions between the recovery rate and other variables. For the secondary outcomes, means were compared using Student's two-tailed *t* test and median were compared using Kruskall-Wallis. Bonferroni correction was applied in case of multiple comparisons of means or medians and level of p-value for reaching statistical significance adjusted accordingly. Multiple linear regression was used to model effect of SMS-RUTF on hemoglobin increase.

Ethical considerations

Permission to conduct the study was obtained from the Ethics Committee of the Catholic University of Bukavu (DRC) and the study was registered prior to staring data collection in the Pan African Clinical Trial Registry (PACTR201303000475166). At the time of admission, each child's parent or carer was informed about the nature and purpose of the study and asked for their verbal and written consent for their child to be included and for their medical information to be used for research purposes. When parents or carer withheld consent for participation, children were referred to one of the four non-participating clinics providing care for SAM in Miti-Murhesa HZ. These clinics were supported by the DRC Government and UNICEF. They used Standard P-RUTF procured from France. The other benefit of participating children included free medical care for any episode of disease during the follow up and one porridge meal per day given to carers when looking after their children at the feeding site.

A data safety monitoring board was assigned to perform an ongoing review of study outcomes based on data extracted by themselves from either the study subject's files or the study database during the bi-monthly visit. The findings served only to decide if the study should be

ended due to an indication of serious side effects. No serious side effects were detected and no reasons for interrupted the study identified.

Results

Enrolment and movement of subjects from preliminary screening to data analysis for the whole cohort and by age category are shown in **Figure 1**. Between March 2013 and February 2014, a total of 924 eligible children were screened, of whom 886 were randomized to either SMS-RUTF (n = 445) or P-RUTF (n = 441) study groups. Thirty-eight eligible children were excluded prior to randomization and another 11 children (6 in the SMS-RUTF group and 5 in the P-RUTF group) withdrew from the study after only one day of attendance after they realized that they could not fulfil the daily attendance requirement. This was classified as "after first day refusal".

Baseline characteristics of children included in the ITT analyses for each study group are shown in **table 3**. Marasmus was the dominant form of SAM among children enrolled into the study and there was no significant difference between groups at baseline for the parameters considered in either of the two age categories.

Program outcomes: recovery, mortality, defaulter and non-response

In children between 24 – 59 months of age the results of the ITT analysis showed that both products met international minimum standards. In the SMS-RUTF group, recovery, mortality, defaulter and non-response rates were 88.3% (204/231), 1.7% (4/231), 7.8% (18/231) and 2.2% (5/231), respectively. In the P-RUTF group the results were 90.3% (214/237), 0.4% (1/237), 7.6% (18/237) and 1.7% (4/237), respectively.

By contrast, in children 6 - 23 months of age the ITT analysis demonstrated that international minimum standards were met for the P-RUTF group but not for the SMS-RUTF group. In this age category the SMS-RUTF group's recovery, mortality, defaulter and non-response rates were 54.3% (113/208), 3.4% (7/208), 24.5% (51/208) and 17.8%(37/208) compared to 75.1% (148/197), 1.0% (2/197), 15.7% (31/197) and 8.1% (16/197) in the P-RUTF group.

Primary outcomes

Both ITT and PP analyses showed that in children aged 24 -59 months the recovery rate (predefine non-inferiority margin Δ = 10%) of the SMS-RUTF group was not inferior to the recovery rate of the P-RUTF group. By contrast, in children aged 6 - 23 months the recovery rate in the SMS-RUTF group was inferior to the recovery rate in the P-RUTF group (**figures 2 and 3**). For weight gain, the PP analysis for weight gain in children who were discharged as recovered showed that the SMS-RUTF group was not inferior to P-RUTF group (predefined non-inferiority margin Δ = 1.2 g/kg/day) in either age category (**Figure 4**). SMS-RUTF was not inferior to P-RUTF in terms of LOS (predefined non-inferiority margin of Δ =14 days) both in ITT analysis and among recovered children (**figure 5**).

Results of the secondary outcomes

Hemoglobin

The unadjusted analysis showed no difference in the means hemoglobin changes between the two RUTF groups for all children evaluated [+1.04(0.79-1.30) g/dl for SMS-RUTF group versus +1.06(0.84,1.28) g/dl a difference of 0.02(-0.31, 0.35) g/dl; p=0.921)] and for those discharged as recovered [+1.23(0.95-1.50) g/dl for SMS-RUTF group versus +1.19(0.90-1.47) g/dl, a difference of 0.04(-0.35, 0.44) g/dl; p=0.837)]. The difference in the proportion of anemic children (hemoglobin<11.0 g/dl) in children discharged as recovered was also not

statistically significant [19/72=26.39% for SMS-RUTF group and 24/80=30.0%, a difference of -3.61(-17.91, 10.69) %; p=0.622)]. The study was underpowered to reach level of statistical significance for differences observed. Linear regression analysis adjusting for age, gender, hemoglobin at admission, daily energy intake from RUTF, LOS in study and growth velocity (supplemental **table 1** for full results of the linear regression) indicated that treatment with SMS-RUTF was associated with a statistically significant greater increase in hemoglobin of 0.670(0.420-0.921)g dl^{-1} when compared to children treated using P-RUTF (p<0.001). The difference of 0.743(0.427–1.059) g dl^{-1} when only children discharged as recovered were included in the analysis was also significant (p<0.001).

Amino acids

At admission the overnight-fasting plasma concentrations of the tested free amino acids did not differ according to the RUTF group. Comparison with community controls children without acute malnutrition showed that malnourished children enrolled in both groups had significantly reduced concentration of several of these AAs (**table 4).** Nutrition rehabilitation with both SMS-RUTF and P-RUTF resulted in the replenishment of all the AAs tested by the time of discharge, except for methionine (table 4). Stratified analyses showed that at the time of discharge, in children aged 6-23 months the deficit was corrected for all the tested AAs, whereas in older children, plasma concentration of both methionine and phenylalanine remained lower than the community controls at the time of discharge (Supplemental **tables 2 and 3**).

Body composition

For children discharged as recovered, there were no differences at discharge between RUTF groups or between the RUTF groups and the community controls in fat mass or fat mass index in the DDT sub-study (**table 5**). By contrast, two by two comparisons of FFM indicated that

children after treatment with either of the two RUTFs had significantly lower levels of FFM than the community controls (Table 5), but this difference disappeared after adjusting for height.

The comparison of the BIA parameters between the sub-samples of SAM children tested at admission and re-tested at the time of reaching MUAC 125mm, showed no significant differences between children in the two intervention groups **(Supplemental table 4)**. However, at discharge from the study, children in the SMS-RUTF group had higher IM and lower FFMI, PhA and Xc/H compared to children in the P-RUTF group **(table 6)**. The SMS-RUTF BIA subgroup also tended to have greater height than the P-RUTF BIA subgroup. Technical challenges (lack of cooperation of children at the beginning of the nutrition rehabilitation or presence of edema) limited the number of children with successful BIA measurement at admission (43 surveyed out of the 200 selected) and at the time of reaching 12.5 cm of MUAC (57 children surveyed out of 200 selected) reducing the statistical power of the BIA analysis at these time points. At discharge, the number of children surveyed was 164 children out of the 200 selected).

Linear growth

Overall in this study there was no clinically relevant catch-up in height for age during treatment and no significant differences in linear growth between the RUTF groups. The severity of stunting in children aged 6 - 23 months at enrolment increased very slightly over the study period, whilst in children aged between 24 - 59 months there was a small but clinically insignificant improvement. Within group analysis showed that the daily increments length gain were not different between children discharged as recovered and children discharged as not-recovered **(Supplemental table 5)**.

RUTF intake, acceptability and tolerance

RUTF intake

The intake of RUTF was higher for children in the P-RUTF group. For children aged 6 - 24 months the mean(SD) daily intake was 183.2 (76.3) g/day for SMS-RUTF versus 207.8 (76.4) g/day for P-RUTF, a difference(95%CI) of = -24.6 (-39.6, -9.6) g/day; p=0.001. For children aged 24 – 59 months the mean(SD) daily intake was 243.8 (86.8) g/day for SMS-RUTF versus 272.7 (77.9) g/day for P-RUTF, a difference(95%CI) of = -28.9(-43.94,-13.9) g/day; p<0.001 **(Supplemental table 6)**

Energy intake was significantly higher in children aged 24-59 month receiving P-RUTF compared to the same age group receiving SMS-RUTF [142.7 (50.8) kcal/kg/day for SMS-RUTF group versus 157.2 (51.9) kcal/kg/day in the P-RUTF group, a difference of -18.63 (-27.65, -9.51); p<0.001. The differences in energy intakes in the younger age group [149.5 (82.9) kcal/kg/day for SMS-RUTF group versus 165.7 (58. 7) kcal/kg/day for P-RUTF a difference of -16.2(-30. 4, -2.0) kcal/kg/day was also significant; p=0.026. Within each RUTF group and each age categories, the daily energy intake did not differ between those who recovered and the non-respondent discharged as non-recovered (data not shown).

RUTF acceptability

The data on RUTF acceptability suggested that the only difference between the two RUTF products was that fewer children below 24 months experienced flatulence on the SMS-RUTF (supplementary table 6). Among those who defaulted, a dislike of the RUTF was reported in 19.2% (14/73) of the SMS-RUTF group versus 13.3% (6.45) in the P-RUTF group; p=0.411. Among the same group side effects related to RUTF intake were 2.74% (2/73) in the SMS-RUTF group versus 2.22% (2/45) in the P-RUTF group; p=0.862.

Discussion

Children with SAM need safe, palatable foods with energy, protein, fat, minerals and vitamins tailored to their needs for restoration of normal body functions and catch up growth(32). Providing P-RUTF tailored to body weight has been shown to successfully support catch-up growth(2;44), but, P-RUTF is expensive and the high cost affects the coverage and the sustainability of CMAM programs. Almost half of the cost of the P-RUTF is due to milk powder that constitutes 25% to 30% of the content of P-RUTF and removing the milk from RUTF has the potential to substantially reduce the cost of such products. Although predicting saving accurately without undertaking actual commercial scale trials is difficult, our analysis in Malawi, where the study foods were produced, suggests a 15% saving on finished product cost. However, the saving is likely to vary from one year to another according to milk price in local and global market and to the country of production.

This study has yielded important information regarding the efficacy of the no milk SMS-RUTF. It has confirmed that SMS-RUTF is not inferior to P-RUTF in children ≥24 months of age with respect to recovery rate, weight gain and length of stay and therefore can be used as an alternative to P-RUTF. Importantly the study has showed that treatment with both SMS and P-RUTFs corrected amino acid deficiencies to a similar extent and both RUTFs were not associated with excess of fat deposition. The BIA sub-study, confirmed substantial increases in the FFMI in both groups bringing them back to a par with the community controls. In the SMS-RUTF group the increase in FFMI was slightly less than in the P-RUTF corresponding to the greater increases in length seen in this group. This minor difference in FFMI was associated by a small difference that is unlikely to have any clinical importance in the markers of FFM quality (phase angle, IM) that were also lower in the SMS-RUTF group, the greater increase in hemoglobin produced by SMS-RUTF compared to P-RUTF also shows that it is

possible to improve the efficacy of RUTF formulations in correcting anemia. At the same time, the study has provided evidence that children aged <24 months don't respond as well to SMS-RUTF and that P-RUTF should continue to be used for this age group until a cheaper alternative is developed.

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The need of animal source food, especially of cow milk products, in food for management of acute malnutrition including moderate and severe acute malnutrition is still subject of an on-going debate (45-49). Several properties of milk including the high quality of the proteins, the presence of bioactive factors, the minerals profile and the high lactose content are given as reasons for the obligatory inclusion of a certain amount of milk in RUTF (49). As a result the current UN guidelines specify that more than 50% of the protein in RUTF should be from an animal source. However, several studies from industrialized countries have shown that in fast growing infants, soya can successfully replace cow milk when there is medical or socio-cultural contraindication to milk (50). Similarly, a study published in 1996 showed that the effectiveness of soya milk and cow milk were similar in nutrition rehabilitation of SAM (51) and we have previously demonstrated that it is possible to achieve the recommended nutrient profile for RUTF without the inclusion of milk (52). The present study confirms our earlier findings from Zambia that an SMS-RUTF containing no animal source protein is as effective as P-RUTF in treating SAM in children 24 months or older(11). This finding has important practical implications, indicating that the cost of the CMAM programs can safely be reduced by using SMS-RUTF in all children above the age of two and restricting the more expensive P-RUTF for use in children less than 2 years of age.

The reasons for the inferior response to the milk-free RUTF in children less than 2 years are not clear. They could be related to one or more factors including differences in

596 energy/nutrient intake, in protein quality, in the prevalence of lactose intolerance, the bio-
597 availability of essential nutrients or physiological responses between the two age groups. We
598 believe that differences in energy intake are unlikely to be important. In a study of adults
599 treated with a Chickpea Sesame RUTF that contained no milk or other animal source protein,
600 there was an excellent correlation between RUTF intake, weight gain and FFM change(53).
601 By contrast, in the present study there was no significant difference of daily intake between
602 the age categories indicating that the poorer response was not the result of any reduction in
603 the intake of energy. In children <2 years of age who did not recover the average RUTF
604 intake was 133 kcal/kg/day and this energy intake, although lower than the recommended
605 intake of 200 kcal/kg/day , should have been sufficient to cover basal metabolic requirements
606 and allow for some growth and recovery. In addition all these children were still breastfed
607 and it is likely that breast milk further contributed to their energy intake. The contribution of
608 breast milk to their nutritional intake is however unknown as although evidence suggests that
609 RUF used for the prevention of malnutrition does not reduce breast milk intake, there is no
610 data on whether this is true when RUTF is prescribed in much larger amount for
611 treatment(54).
612
613 Differences in protein quality between SMS-RUTF and P-RUTFs combined with a greater
614 requirement for certain amino acids in young children cannot be ruled out as a cause of the
615 inferior response to the milk-free RUTF in children less than 2 years. SMS-RUTF had a lower
616 content of tyrosine, methionine and proline than the P-RUTF. The mean daily SMS-RUTF
617 intake in children discharge as "non-recovered" corresponded to a daily intake of 121
618 mg/kg/day of tyrosine and 52 mg/kg/day methionine. These intakes are greater than the 99
619 mg/kg/day of tyrosine that Badaloo et al. estimated was needed to support catch-up growth of
620 g/kg/day (55), above the 38 mg/kg/day of methionine required by formula fed infants who

grow at more than10 g/kg/day (56). The increased plasma levels of free amino acids between admission and discharge and compared to those seen in community controls indicates that the two RUTFs supplied sufficient quantity of these amino acids. However, we did not measure all the amino acids and the sample size did not allow testing a sufficient number of non-recovered children. Thus, future research should still assess possible contribution of some key amino acids in the poor physical growth in children below 24 months recovering from SAM.

A decreased bio-availability of essential nutrients is another possible cause for the inferior response to the milk-free RUTF in the younger children. Phytic acid is a common plant storage compound that binds divalent metallic ions preventing their absorption in the small intestine that is not present in animal source foods. It is therefore theoretically possible that the switch from milk to the grains and legumes could have increased the phytic acid content of the SMS-RUTF decreasing the bio-availability of iron and zinc. We believe that this is explanation is however unlikely. A recent laboratory analysis of different P-RUTFs found huge variations in the phytic acid levels, that ranged from 1015mg/100g for P-RUTF produced in Europe down to 371 mg/100g for P-RUTF manufactured in African countries (57). The iron content of 10-14 mg/100g in the P-RUTF combined with these amounts of phytic acid give phytic acid/iron ratios between 7– 13, far higher than the recommended upper limit ratio of <1(58). By contrast, the production of SMS-RUTF included specific measures to reduce phytic acid and to increase the content of iron. This resulted in a phytic acid acid/iron ratio of 0.8. Based on evidence that increasing vitamin C improves absorption of iron (59;60), the vitamin C content of the SMS was also increased to enhance the iron bioavailability. The greater increase in hemoglobin amongst children receiving SMS-RUTF suggests that these measures were effective in increasing iron absorption. The SMS-RUTF also included more zinc compared to P-RUTF in order to bring the phytic acid/zinc ratios towards international recommendations (see table 1). Specific iron and zinc absorption

studies should be done to confirm that the strategy used to improve bioavailability of these minerals was sufficient.

Several studies have reported that tolerance of lactose declines naturally with age with the prevalence of lactose intolerance increases sharply after the cessation breastfeeding at round 24 months of age (61;62). Indeed, post weaning genetically programmed and irreversible reduction of lactase activity has been described worldwide (63). Thus increasing lactose intolerance in the older children could explain the differences seen with the benefit of the growth promoting nutrients present in milk increasingly counterbalanced by the negative effect of lactose intolerance in the older children. However, as the response to treatment in both the study arms was superior amongst children ≥24 months this explanation is unlikely. , a conclusion supported by the fact that several studies have previously reported similar growth pattern in lactose intolerant children given lactose free dairy products compared to lactose intolerant children given dairy products containing lactose (61;62).

Differences in the pathophysiology of SAM between the two age groups is likely to be important in both the inferior response in the treatment of SAM and also the different the linear growth response of the younger and older children that we observed. In this study, the length for age in children below 24 months of age continued to decline during nutrition treatment whereas in the older children some linear growth catch up was observed during treatment. This suggest that the nutrient requirement for rehabilitation may not be the same for children off different ages and it is likely that similar physiological differences are also important reasons behind the inferior response to the milk-free RUTF in the younger children. These findings highlight the need to enhance our understanding of the differences between younger and older SAM children, including differences in biochemical parameters, in nutrient

671 requirements, body composition at different stage of acute malnutrition as well as the precise
672 composition of weight gain at different time of the recovery process. Such information is
673 likely to facilitate the adjustment of RUTF composition with the aim of developing a product
674 capable of reversing both wasting and stunting, especially in children below 24 months.
675

676 In this study there was a significantly greater increase in hemoglobin with no evidence of
677 increased morbidity using an RUTF with an iron content approximately four times greater
678 than that currently recommended. This suggests a need to revise the current recommendation
679 and increase iron density in RUTF. Historically fears that iron might induce the formation of
680 free radicals that could not be detoxified in children with SAM meant that the iron content of
681 RUTF was kept low(64;65). More recently new concerns related to the promotion of
682 pathogenic bacteria in the gut that some studies have attributed to iron fortified food (66;67)
683 have served to keep the iron content of RUTF down(68-70). However, other studies have
684 shown that increasing iron levels in nutritional supplements has positive effects on growth
685 (71) and on hemoglobin (72) as well as indicating that iron can be safely prescribed to
686 children recovering from severe malaria, a condition that in the past has been associated with
687 very high post-discharge mortality (73;74). An unpublished study conducted in Senegal also
688 showed that during the treatment of SAM using P-RUTF with the current recommended iron
689 density hemoglobin went up by 0.17 g/dl compared to an increase of 0.83 g/dl in those
690 receiving F100 therapeutic milk fortified with iron to provide 3mg/kg/ day(75). It is
691 important to note that even at the increased iron dosage used in the SMS-RUTF there were
692 still a high proportion of anemic children at discharge and it is likely that any solution to the
693 problems of anemia in SAM will require a mechanism to increase iron intake for several
694 months post discharge. To the best of our knowledge, this is the first study using the reference
695 two compartments model technique for the determination of body composition (DDT

696 approach), showing that the use of RUTF for nutrition rehabilitation of SAM children is not
697 associated with excess deposition of fat. All previous studies that evaluated this issue were
698 done in program using milk based diet (76-78). These studies showed that nutrition therapy
699 with appropriately fortified milk diet is not associated with excesses in fat mass deposition
700 (76-78). However, despite these publications there has been a continued debate around the
701 possible association between rapid weight catch up growth observed during nutrition
702 rehabilitation of SAM and higher amounts of body fat deposition and insufficient repletion of
703 muscle and visceral proteins(78-82). Our findings show no excess fat deposition either with
704 SMS-RUTF or with P-RUTF when compared to community controls and that at the time of
705 discharge the absolute fat mass in children who had met anthropometric discharge criteria was
706 similar to community controls. These results confirm the findings of a recently published
707 study conducted in Kampala (Uganda) that, through the use of serum leptin level as proxy
708 biomarker of fat reserves, demonstrated that fat replenishment is completed first and early
709 during nutrition rehabilitation, before the anthropometric discharge criteria are met (83).
710
711 Our results also show that at the time these children meet anthropometric criteria for recovery
712 they still have deficits of FFM when compared to the community controls. This indicates that
713 at current best practice SAM treatment regimens combined with the use of the internationally
714 accepted discharge criteria are not necessarily sufficient to re-establish FFM. This important
715 finding provides a rationale for the persisting increased risk of death in children who are
716 treated and attain “anthropometric cure” in tertiary hospitals after admission at an advanced
717 stage of wasting and metabolic adaptation (84;85). It also maybe helps to explain the much
718 lower long term mortality risk post discharge of those admitted to community based programs
719 at an earlier stage of the progression of SAM.(84).
720

In this study the fat mass and the FFMI of children who recovered was comparable to that of the community controls, suggesting that the differences in the absolute amounts of FFM could be explained by differences in height. It is therefore possible the residual increased risk of mortality post discharge after the treatment of SAM may be related to the degree of stunting(86). The close inter-connections between acute and chronic malnutrition combined with the relatively limited impact of short duration treatment with RUTF on stunting supports the need to investigate integrated approaches towards acute and chronic malnutrition (87-89). Such approaches that combine intensive initial nutrition rehabilitation to correct weight/muscle deficit and prolonged nutrition support to re-establish FFM and sustain recovery of linear deficit should be developed and their effectiveness in preventing relapse and promoting linear growth and FFM catch ups assessed.

BIA analysis gave similar results to DDT regarding change in body fat, Fat Free mass and Fat Free mass index. In addition the BIA analysis identified significant differences in cellular membranes function indicators such as phase angle and wellness marker between children treated with SMS-RUTF and those treated with P-RUTF. The clinical significance of the observed differences is unknown and need further investigations but many studies have demonstrated that Phase angle is an independent predictor of diseases and death in both children and adults (90-94).

This study was conducted in a setting where all the ingredients are already commonly used in the preparation of porridge for complementary feeding. Despite that, our findings can be generalized as soya and maize have been used in food distributed during humanitarian crises worldwide and existing evidence shows that the standard RUTFs is effective in children 6 to 59 months of age suffering from SAM of all continents even where peanut paste is not

commonly used in feeding infant and young children. Also, we enrolled children using criteria universally used for enrollment in CMAM programs. However, our findings should be interpreting taking into account some limitations. The main limitation is that we were unable to measure the total daily nutritional intake and measured instead only RUTF intake. Measuring total daily intake would have allowed us to better distinguish the effect of product composition on satiety on the response observed in both under twos and over twos. Although we doubt that the intake from home food or breast milk influenced the recovery, we were unable to exclude it definitively. The second limitation is that we were unable to include sufficient number of children who did not recover into the sub-studies evaluating the evolution of amino acid profile or assessing body composition to allows determine if differences in food quality such us in amino acid profile contributed to the differences observed.

In conclusion, the present study has demonstrated that SMS-RUTF can be used to treat SAM in children ≥24 months of age and that the iron content in RUTF should be increased. The lower cost of manufacture of SMS-RUTF and its reliance on locally grown ingredients would reduce the costs of CMAM programs and facilitate the production of RUTF in countries with a high burden of SAM, especially because we have placed this recipe in the public domain and put in place mechanisms preventing any entity from blocking access to it. The additional iron would increase the efficacy of the product in the treatment of anemia associated with SAM.

The study has also shown that there is a need for two products with different composition to treat SAM. One for children under 2 years that ideally should also be optimized to promote a reversal of stunting and one for the older children that should be formulated to maintain efficacy but reduce costs. Cost-effectiveness analyses and the assessment of the impact on

771 program logistic are needed to guide the final decision. More research is required to identify
772 the reasons for the lower recovery rate with SMS-RUTF in younger children. Hypotheses to
773 be explored include higher satiety with SMS-RUTF, lower breast milk intake, sub-optimal
774 absorption of some key micronutrients and difference in key amino acids. More research in
775 also needed on products that better address stunting in this younger age group.
776

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Conflict of interest:

Valid Nutrition designed and produced the SMS-RUTF. PA is an employee of Valid Nutrition. SC is the unpaid director of Valid Nutrition. Valid International is the sister company of Valid Nutrition and BP and KS are Valid International employee. All the others authors have no conflict of interest. The PRANA foundation and Irish Aid had no say on the design, implementation and interpretation of the results. Valid Nutrition administered the study grant. Valid Nutrition and Valid international researchers participated in study design and implementation and in the interpretation of results.

792

793 **Contribution of authors**:

794 SC, KS, PA and PB conceived study idea, designed SMS-RUTF and provided technical
795 oversight throughout the trial including data collection, data analysis and preparation of this
796 manuscript. BB, CNM contributed to the study design and data collection tools development
797 and implemented data collection and entry. JCKW and MDW participate in the analysis of
798 the data and the interpretation of findings. All authors contributed to the write up of the
799 manuscript. All authors have read and approved the manuscript.

Reference List

1. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de OM, Ezzati M, Grantham-McGregor S, Katz J, Martorell R et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427-51.

2. Collins S, Dent N, Binns P, Bahwere P, Sadler K, Hallam A. Management of severe acute malnutrition in children. Lancet 2006;368:1992-2000.

3. Collins, S. Community-based therapeutic care: A new paradigm for selective feeding in nutritional crises. 48. 2004. London, Humanitarian Practice Network, Overseas Development Institute. Network Paper.

Ref Type: Report

4. Bahwere P, Piwoz E, Joshua MC, Sadler K, Grobler-Tanner CH, Guerrero S, Collins S. Uptake of HIV testing and outcomes within a Community-based Therapeutic Care (CTC) programme to treat severe acute malnutrition in Malawi: a descriptive study. BMC Infect Dis 2008;8:106.

5. Briend A, Lacsala R, Prudhon C, Mounier B, Grellety Y, Golden MHN. Ready-to-use therapeutic food for treatment of marasmus [letter]. Lancet 1999;353:1767-8.

6. Manary MJ. Local production and provision of ready-to-use therapeutic food (RUTF) spread for the treatment of severe childhood malnutrition. Food Nutr Bull 2006;27:S83-S89.

7. WHO. Management of severe malnutrition: A manual for physicians and other senior health workers. Geneva: WHO, 1999.

8. Rogers E, Myatt M, Woodhead S, Guerrero S, Alvarez JL. Coverage of community-based management of severe acute malnutrition programmes in twenty-one countries, 2012-2013. PLoS One 2015;10:e0128666.

9. Collins S, Sadler K. Outpatient care for severely malnourished children in emergency relief programmes: a retrospective cohort study. Lancet 2002;360:1824-30.

10. Diop EHI, Dossou NI, Ndour MM, Briend A, Wade S. Comparison of the efficacy of a solid ready to use food and a liquid milk-based diet for the rehabilitation of severely malnourished children: a randomized trial. Am J Clin Nutr 2003;302-7.

11. Irena AH, Bahwere P, Owino VO, Diop EI, Bachmann MO, Mbwili-Muleya C, Dibari F, Sadler K, Collins S. Comparison of the effectiveness of a milk-free soy-maize-sorghum-based ready-to-use therapeutic food to standard ready-to-use therapeutic food with 25% milk in nutrition management of severely acutely malnourished Zambian children: an equivalence non-blinded cluster randomised controlled trial. Matern Child Nutr 2013.

12. Action Contre la Faim. Enquete Nutrionnelle Anthropométrique 2011: Zone de Santé de Miti-Murhesa. 2011.

Ref Type: Report

13. Balaluka GB, Nabugobe PS, Mitangala PN, Cobohwa NB, Schirvel C, Dramaix MW, Donnen P. Community volunteers can improve breastfeeding among children under six months of age in the Democratic Republic of Congo crisis. Int Breastfeed J 2012;7:2.

14. Bisimwa G, Mambo T, Mitangala P, Schirvel C, Porignon D, Dramaix M, Donnen P. Nutritional monitoring of preschool-age children by community volunteers during armed conflict in the Democratic Republic of the Congo. Food Nutr Bull 2009;30:120-7.

15. Vis HL, Pourbaix P, Thilly C, Van der Borght H. [Analysis of the nutritional situation of traditionalsocieties of the Kivu Lake region: the Shi and the Havu. Study of food consumption]. Ann Soc Belges Med Trop Parasitol Mycol 1969;49:353-419.

16. Nicoll A. Integrated management of childhood illness in resource-poor countries: an initiative from the World Health Organization. Trans R Soc Trop Med Hyg 2000;94:9-11.

17. Republique Democratique du Congo, Ministere de la Sante. Protocol National de la prise en charge integree de la malnutrition aigue. 2011.
Ref Type: Generic

18. World Health Organization. Training Course on Child Growth Assessment. Geneva: WHO, 2008.[WHO website]. 2008.
Ref Type: Generic

19. Bertani R, Sergi G, Lupoli L, Berton A, Volpato S, Zambon K, Coin A, Enzi G. Measurement of total body water (TBW) through in vivo dilution of tracer compounds: use of D2O and its determination by FT infrared spectroscopy. Ann Chim 2002;92:135-8.

20. Girma T, Kaestel P, Workeneh N, Molgaard C, Andersen GS, Michaelsen KF, Friis H, Wells JC. Biompedance index for measurement of total body water in severely malnourished children children: assessing the effect of nutritional oedema. Clinical Nutrition 2015;in press.

21. Fomon SJ, Haschke F, Ziegler EE, Nelson SE. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 1982;35:1169-75.

22. Imaizumi A, Shimba N, Yoshida H et al. Clinical Implementation of Metabolomics. INTECH Open Access Publisher, 2012.

23. Yoshida H, Kondo K, Yamamoto H, Kageyama N, Ozawa S, Shimbo K, Muramatsu T, Imaizumi A, Mizukoshi T, Masuda J et al. Validation of an analytical method for human plasma free amino acids by high-performance liquid chromatography ionization mass spectrometry using automated precolumn derivatization. J Chromatogr B Analyt Technol Biomed Life Sci 2015;998-999:88-96.

24. Bahwere P, Deconinck H, Banda T, Mtimuni A, Collins S. Impact of household food insecurity on the nutritional status and the response to therapeutic feeding of people living with human immunodeficiency virus. Patient Prefer Adherence 2011;5:619-27.

25. Bahwere P, Banda T, Sadler K, Nyirenda G, Owino V, Shaba B, Dibari F, Collins S. Effectiveness of milk whey protein-based ready-to-use therapeutic food in treatment of severe acute malnutrition in Malawian under-5 children: a randomised, double-blind, controlled non-inferiority clinical trial. Matern Child Nutr 2014.

26. Bahwere P, Deconinck H, Banda T, Collins S. Effective Therapeutic Feeding with Chickpea Sesame Based Ready-to-Use Therapeutic Food (CS-RUTF) in Wasted Adults with Confirmed or Suspected AIDS. WORLD 2011;1:169-81.

27. Kerac M, Bunn J, Seal A, Thindwa M, Tomkins A, Sadler K, Bahwere P, Collins S. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): a double-blind efficacy randomised controlled trial in Malawi. Lancet 2009;374:136-44.

28. Flax VL, Maleta K, Ashorn U, Manary MJ, Briend A, Ashorn P. Intake of lipid-based nutrient supplements during illness and convalescence among moderately-underweight Malawian children. J Health Popul Nutr 2008;26:468-70.

29. Kayira D, Bentley ME, Wiener J, Mkhomawanthu C, King CC, Chitsulo P, Chigwenembe M, Ellington S, Hosseinipour MC, Kourtis AP et al. A lipid-based nutrient supplement mitigates weight loss among HIV-infected women in a factorial randomized trial to prevent mother-to-child transmission during exclusive breastfeeding. Am J Clin Nutr 2012;95:759-65.

30. Parker ME, Bentley ME, Chasela C, Adair L, Piwoz EG, Jamieson DJ, Ellington S, Kayira D, Soko A, Mkhomawanthu C et al. The acceptance and feasibility of replacement feeding at 6 months as an HIV prevention method in Lilongwe, Malawi: results from the BAN study. AIDS Educ Prev 2011;23:281-95.

31. Gibson RS, Bailey KB, Gibbs M, Ferguson EL. A review of phytate, iron, zinc, and calcium concentrations in plant-based complementary foods used in low-income countries and implications for bioavailability. Food Nutr Bull 2010;31:S134-S146.

32. WHO, UNICEF, and SCN. Joint statement on the community-based management of severe malnutrition in children. 2007.
Ref Type: Hearing

33. Schwartz J, Dube K, Sichert-Hellert W, Kannenberg F, Kunz C, Kalhoff H, Kersting M. Modification of dietary polyunsaturated fatty acids via complementary food enhances n-3 long-chain polyunsaturated fatty acid synthesis in healthy infants: a double blinded randomised controlled trial. Arch Dis Child 2009;94:876-82.

34. Pereira DI, Irving SSC, Lomer MC, Powell JJ. A rapid, simple questionnaire to assess gastrointestinal symptoms after oral ferrous sulphate supplementation. BMC gastroenterology 2014;14:103.

35. Nyeko R, Kalyesubula I, Mworozi E, Bachou H. Lactose intolerance among severely malnourished children with diarrhoea admitted to the nutrition unit, Mulago hospital, Uganda. BMC Pediatr 2010;10:31.

36. SealedEnvelope. SealedEnvelope. 2015.
Ref Type: Computer Program

37. Julious SA. Sample sizes for clinical trials with normal data. Stat Med 2004;23:1921-86.

38. Julious SA, Campbell MJ. Tutorial in biostatistics: sample sizes for parallel group clinical trials with binary data. Stat Med 2012;31:2904-36.

39. Lauritsen.J.M and Bruus.M. Epidata entry version 3.02:A comprehensive tool for validated entry and documentation of data.. (3.02). 2003. The Epidata Association.
Ref Type: Computer Program

40. StataCorp, L. P. College Station, TX. 2011. StataCorp.
Ref Type: Generic

41. Bozzetto S, Piccoli A, Montini G. Bioelectrical impedance vector analysis to evaluate relative hydration status. Pediatr Nephrol 2010;25:329-34.

42. Le Henanff A, Giraudeau B, Baron G, Ravaud P. Quality of reporting of noninferiority and equivalence randomized trials. JAMA 2006;295:1147-51.

43. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006;295:1152-60.

44. Collins S, Sadler K, Dent N, Khara T, Guerrero S, Myatt M, Saboya M, Walsh A. Key issues in the success of community-based management of severe malnutrition. Food Nutr Bull 2006;27:S49-S82.

45. Ferguson EL, Briend A, Darmon N. Can optimal combinations of local foods achieve the nutrient density of the F100 catch-up diet for severe malnutrition? J Pediatr Gastroenterol Nutr 2008;46:447-52.

46. Golden BE, Golden MH. Plasma zinc, rate of weight gain, and the energy cost of tissue deposition in children recovering from severe malnutrition on a cow's milk or soya protein based diet. Am J Clin Nutr 1981;34:892-9.

47. Hoppe C, Andersen GS, Jacobsen S, Molgaard C, Friis H, Sangild PT, Michaelsen KF. The use of whey or skimmed milk powder in fortified blended foods for vulnerable groups. J Nutr 2008;138:145S-61S.

48. Michaelsen KF, Hoppe C, Roos N, Kaestel P, Stougaard M, Lauritzen L, Molgaard C, Girma T, Friis H. Choice of foods and ingredients for moderately malnourished children 6 months to 5 years of age. Food Nutr Bull 2009;30:S343-S404.

49. Michaelsen KF, Nielsen AL, Roos N, Friis H, Molgaard C. Cow's milk in treatment of moderate and severe undernutrition in low-income countries. Nestle Nutr Workshop Ser Pediatr Program 2011;67:99-111.

50. Vandenplas Y, Castrellon PG, Rivas R, Gutierrez CJ, Garcia LD, Jimenez JE, Anzo A, Hegar B, Alarcon P. Safety of soya-based infant formulas in children. Br J Nutr 2014;111:1340-60.

51. de Oliveira JE, Scatena L, Netto NO, Duarte GG. The nutritive value of soya milk and cow's milk in malnourished children: a comparative study. J Pediatr 1966;69:670-5.

52. Dibari F, Diop el HI, Collins S, Seal A. Low-cost, ready-to-use therapeutic foods can be designed using locally available commodities with the aid of linear programming. J Nutr 2012;142:955-61.

53. Bahwere P, Sadler K, Collins S. Acceptability and effectiveness of chickpea sesame-based ready-to-use therapeutic food in malnourished HIV-positive adults. Patient Preference and Adherence 2009.

54. Owino VO, Bahwere P, Bisimwa G, Mwangi CM, Collins S. Breast-milk intake of 9-10-mo-old rural infants given a ready-to-use complementary food in South Kivu, Democratic Republic of Congo. Am J Clin Nutr 2011;93:1300-4.

55. Badaloo A, Hsu JW, Taylor-Bryan C, Reid M, Forrester T, Jahoor F. Tyrosine requirement during the rapid catch-up growth phase of recovery from severe childhood undernutrition. Br J Nutr 2010;104:1174-80.

56. Huang L, Hogewind-Schoonenboom JE, van Dongen MJ, de GF, Voortman GJ, Schierbeek H, Twisk JW, Vermes A, Chen C, Huang Y et al. Methionine requirement of the enterally fed term infant in the first month of life in the presence of cysteine. Am J Clin Nutr 2012;95:1048-54.

57. Roos N, Sorensen JC, Sorensen H, Rasmussen SK, Briend A, Yang Z, Huffman SL. Screening for anti–nutritional compounds in complementary foods and food aid products for infants and young children. Maternal & child nutrition 2013;9:47-71.

58. Hurrell RF. Phytic acid degradation as a means of improving iron absorption. Int J Vitam Nutr Res 2004;74:445-52.

59. Troesch B, Egli I, Zeder C, Hurrell RF, Zimmermann MB. Fortification iron as ferrous sulfate plus ascorbic acid is more rapidly absorbed than as sodium iron EDTA but neither increases serum nontransferrin-bound iron in women. The Journal of Nutrition 2011;141:822-7.

60. Cercamondi CI, Egli IM, Mitchikpe E, Tossou F, Hessou J, Zeder C, Hounhouigan JD, Hurrell RF. Iron bioavailability from a lipid-based complementary food fortificant mixed with millet porridge can be optimized by adding phytase and ascorbic acid but not by using a mixture of ferrous sulfate and sodium iron EDTA. The Journal of Nutrition 2013;143:1233-9.

61. Erinoso HO, Hoare S, Spencer S, Lunn PG, Weaver LT. Is cow's milk suitable for the dietary supplementation of rural Gambian children? 1. Prevalence of lactose maldigestion. Ann Trop Paediatr 1992;12:359-65.

62. Brown KH, Parry L, Khatun M, Ahmed G. Lactose malabsorption in Bangladeshi village children: relation with age, history of recent diarrhea, nutritional status, and breast feeding. Am J Clin Nutr 1979;32:1962-9.

63. Wang Y, Harvey CB, Hollox EJ, Phillips AD, Poulter M, Clay P, Walker-Smith JA, Swallow DM. The genetically programmed down-regulation of lactase in children. Gastroenterology 1998;114:1230-6.

64. Dempster WS, Sive AA, Rosseau S, Malan H, Heese HV. Misplaced iron in kwashiorkor. Eur J Clin Nutr 1995;49:208-10.

65. Golden MHN, Ramdath D. Free radicals in the pathogenesis of kwashiorkor. Proceedings of the nutritional society 1987;46:53-68.

66. Soofi S, Cousens S, Iqbal SP, Akhund T, Khan J, Ahmed I, Zaidi AK, Bhutta ZA. Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial. The Lancet 2013;382:29-40.

67. Zimmermann MB, Chassard C, Rohner F, N'Goran EzK, Nindjin C, Dostal A, Utzinger J+, Ghattas H, Lacroix C, Hurrell RF. The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire. The American journal of clinical nutrition 2010;92:1406-15.

68. Bernal C, Velasquez C, Alcaraz G, Botero J. Treatment of severe malnutrition in children: experience in implementing the World Health Organization guidelines in Turbo, Colombia. J Pediatr Gastroenterol Nutr 2008;46:322-8.

69. Golden MH. Proposed recommended nutrient densities for moderately malnourished children. Food Nutr Bull 2009;30:S267-S342.

70. Jayatissa R, Bekele A, Kethiswaran A, De Silva AH. Community-based management of severe and moderate acute malnutrition during emergencies in Sri Lanka: challenges of implementation. Food Nutr Bull 2012;33:251-60.

71. Troesch B, van Stuijvenberg ME, Smuts CM, Kruger HS, Biebinger R, Hurrell RF, Baumgartner J, Zimmermann MB. A micronutrient powder with low doses of highly absorbable iron and zinc reduces iron and zinc deficiency and improves weight-for-age Z-scores in South African children. J Nutr 2011;141:237-42.

72. Lopriore C, Guidoum Y, Briend A, Branca F. Spread fortified with vitamins and minerals induces catch-up growth and eradicates severe anemia in stunted refugee children aged 3-6 y. Am J Clin Nutr 2004;80:973-81.

73. Glinz D, Kamiyango M, Phiri KS, Munthali F, Zeder C, Zimmermann MB, Hurrell RF, Wegm++ller R. The effect of timing of iron supplementation on iron absorption and haemoglobin in post-malaria anaemia: a longitudinal stable isotope study in Malawian toddlers. Malaria journal 2014;13:397.

74. Phiri KS, Calis JC, Faragher B, Nkhoma E, Ng'oma K, Mangochi B, Molyneux ME, van Hensbroek MB. Long term outcome of severe anaemia in Malawian children. PLoS ONE 2008;3:e2903.

75. Diop, El H. I., Dossou, N. I., Ndour, M. M., Briend, Andre, and Wade, S. Hemoglobin variations during nutrition rehabilitation of severely malnourished children with a solid or liquid diet with different level of iron. 20-2-2003.

Ref Type: Unpublished Work

76. Branca F, Robins SP, Ferro-Luzzi A, Golden MHN. Bone turnover in malnourished children. Lancet 1992;340:1493-6.

77. Fjeld CR, Schoeller DA, Brown KH. Body composition of children recovering from severe protein-energy malnutrition at two rates of catch-up growth. Am J Clin Nutr 1989;50:1266-75.

78. Radhakrishna KV, Kulkarni B, Balakrishna N, Rajkumar H, Omkar C, Shatrugna V. Composition of weight gain during nutrition rehabilitation of severely under nourished children in a hospital based study from India. Asia Pac J Clin Nutr 2010;19:8-13.

79. Castilla-Serna L, Perez-Ortiz B, Cravioto J. Patterns of muscle and fat mass repair during recovery from advanced infantile protein-energy malnutrition. Eur J Clin Nutr 1996;50:392-7.

80. Golden MH, Golden BE. Effect of zinc supplementation on the dietary intake, rate of weight gain, and energy cost of tissue deposition in children recovering from severe malnutrition. Am J Clin Nutr 1981;34:900-8.

81. Graham GG, MacLean WC, Jr., Brown KH, Morales E, Lembcke J, Gastanaduy A. Protein requirements of infants and children: growth during recovery from malnutrition. Pediatrics 1996;97:499-505.

82. Spady DW, Payne PR, Picou D, Waterlow JC. Energy balance during recovery from malnutrition. Am J Clin Nutr 1976;29:1073-88.

83. Bartz S, Mody A, Hornik C, Bain J, Muehlbauer M, Kiyimba T, Kiboneka E, Stevens R, Bartlett J, Peter JVS. Severe acute malnutrition in childhood: hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. The Journal of Clinical Endocrinology & Metabolism 2014.

84. Bahwere P, Mtimuni A, Sadler K, Banda T, Collins S. Long term mortality after community and facility based treatment of severe acute malnutrition: Analysis of data from Bangladesh, Kenya, Malawi and Niger. Journal of Public Health and Epidemiology 2012;4:215-25.

85. Kerac M, Bunn J, Chagaluka G, Bahwere P, Tomkins A, Collins S, Seal A. Follow-Up of Post-Discharge Growth and Mortality after Treatment for Severe Acute Malnutrition (FuSAM Study): A Prospective Cohort Study. PLoS ONE 2014;9:e96030.

86. Briend A, Khara T, Dolan C. Wasting and stunting—similarities and differences: Policy and programmatic implications. Food & Nutrition Bulletin 2015 (in press).

87. Briend A, Garenne M, Maire B, Fontaine O, Dieng K. Nutritional status, age and survival: the muscle mass hypothesis. Eur J Clin Nutr 1989;43:715-26.

88. Heymsfield SB, Stevens V, Noel R, McManus C, Smith J, Nixon D. Biochemical composition of muscle in normal and semistarved human subjects: relevance to anthropometric measurements. Am J Clin Nutr 1982;36:131-42.

89. Khara, T. and Dolan, C. Technical Briefing paper: Association between wasting and stunting, policy, programming and research implications. Oxford, Emergency Nutrition Network (ENN).
Ref Type: Generic

90. Gupta D, Lammersfeld CA, Burrows JL, Dahlk SL, Vashi PG, Grutsch JF, Hoffman S, Lis CG. Bioelectrical impedance phase angle in clinical practice: implications for prognosis in advanced colorectal cancer. Am J Clin Nutr 2004;80:1634-8.

91. Wells JC, Williams JE, Fewtrell M, Singhal A, Lucas A, Cole TJ. A simplified approach to analysing bio-electrical impedance data in epidemiological surveys. Int J Obes (Lond) 2007;31:507-14.

92. Richter E, Denecke A, Klapdor S, Klapdor R. Parenteral nutrition support for patients with pancreatic cancer--improvement of the nutritional status and the therapeutic outcome. Anticancer Res 2012;32:2111-8.

93. Lee SY, Lee YJ, Yang JH, Kim CM, Choi WS. The Association between Phase Angle of Bioelectrical Impedance Analysis and Survival Time in Advanced Cancer Patients: Preliminary Study. Korean J Fam Med 2014;35:251-6.

94. Norman K, Stobaus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. Clin Nutr 2012;31:854-61.

Table 1: Ingredients and nutrients of the study foods

Ingredients/Nutrients		SMS-RUTF[1]	P-RUTF[2]	UN specifications[3]
Ingredients				
Soybean , dehulled	(g/100g)	38.6	0.0	
Maize, degerminated	(g/100g)	4.0	0.0	
Sorghum, white, whole grain	(g/100g)	10.0	0.0	
Dried Skim Milk(g/100g)		0.0	25.0	
Sugar	(g/100g)	16.7	27.4	
Peanut paste	(g/100g)	0.0	26.0	
Palm Oil	(g/100g)	21.6	20.0	
Linseed oil	(g/100g)	2.1	0.0	
Palm stearin	(g/100g)	4.0	0.0	
Vitamin and minerals Premix	(g/100g)	3.0	1.6	
Nutrients				
Energy	(kcal/100g)	553	530	520-550
Protein/Energy ratio	(%)	11.9	12	10-12
Fat/Energy ratio	(%)	59.1	56.0	45-60
Omega-6/Energy ratio	(%)	12.3		3-10
Omega-3/Energy ratio	(%)	3.1		0.3-2.5
Omega-6/Omega-3 ratio		4.0		5-9
Vitamin A	(µg/100g)	1000	910	810-1100
Vitamin C	(mg/100g)	329	53	≥50
Vitamin D	(µg/100g)	14	16	15-20
Vitamin E	(mg/100g)	40.7	20	≥20
Thiamin (Vitamin B1)	(mg/100g)	1.4	0.6	≥0.5
Riboflavin (Vitamin B2)	(mg/100g)	1.9	1.8	≥1.6
Niacin (Vitamin B3)	(mg/100g)	19	5.3	≥5
Pantothenic acid (Vitamin B5)	(mg/100g)	8.3	3.1	≥3
Pyridoxine (Vitamin B6)	(mg/100g)	1.4	0.6	≥0.6
Biotin (Vitamin B7)	(µg/100g)	56	65	≥60
Folates (Vitamin B9)	(µg/100g)	370	210	≥200
Cobalamin (Vitamin B12)	(µg/100g)	4.3	1.8	≥1.6
Vitamin K	(µg/100g)	14	21	15-30
Calcium	(mg/100g)	437.8	315	300-600
Phosphorus	(mg/100g)	446.0	370	300-600
Magnesium	(mg/100g)	74	86	60-140
Potassium	(mg/100g)	1155.8	1140	1100-1400
Copper	(mg/100g)	0.9	1.7	1.4-1.8
Iodine	(µg/100g)	417	100	70-140
Iron	(mg/100g)	43.8	12	10-14
Zinc	(mg/100g)	18.5	11.1	11-14
Anti-nutrients				
Phytic acid	(mg/100g)	420	255	<100
Phytic acid/Zinc ratio		2.0	2.2	<15
Phytic acid/Iron ratio		0.8	1.9	<1

[1]SMS-RUTF=Soya-Maize-Sorghum Based Ready-To-Use Therapeutic Food; [2]P-RUTF=

Peanut paste based Ready-To-Use Therapeutic Food; [3]Obtained from references 4, 15 and 16.

Table 2: Comparison of the amino acid profile of the study Ready-To-Use Therapeutic foods obtained by laboratory analysis

Amino acid (g/100g)	SMS-RUTF[2]	P-RUTF[3]	SMS-RUTF/P-RUTF ratio	Adjusted[1] SMS-RUTF/P-RUTF ratio
Cystine	0.31	0.18	1.72	1.54
Methionine	0.22	0.25	0.88	0.78
Aspartic Acid	1.95	1.39	1.40	1.24
Threonine	0.70	0.54	1.30	1.16
Serine	0.94	0.82	1.15	1.02
Glutamic Acid	3.24	3.01	1.08	0.96
Glycine	0.74	0.53	1.40	1.25
Alanine	0.81	0.52	1.56	1.37
Valine	0.77	0.71	1.08	0.96
Isoleucine	0.77	0.60	1.28	1.14
Leucine	1.41	1.20	1.12	1.03
Tyrosine	0.51	0.56	0.91	0.81
Phenylalanine	0.86	0.72	1.19	1.06
Lysine	1.05	0.93	1.30	1.01
Histidine	0.46	0.37	1.24	1.11
Arginine	1.21	1.01	1.20	1.08
Proline	0.94	1.07	0.88	0.79
Tryptophan	0.24	0.20	1.20	1.07

[1]adjusted by using the true protein digestibility for soybean flour, sorghum flour and corn flour for the SMS-RUTF and Milk and peanut butter for the P-RUTF; [2]SMS-RUTF=Soya-Maize-Sorghum Based Ready-To-Use Therapeutic Food; [3]P-RUTF= Peanut paste based Ready-To-Use Therapeutic Food;

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Table 3: Baseline characteristics for children included in the Intention-To-Treat analysis

Criteria	6-23 months		24-59 months	
	SMS-RUTF[1]	P-RUTF[2]	SMS-RUTF[1]	P-RUTF[2]
n	208	197	231	237
Socio-demographic parameters				
Male, n(%)	110(52.9)	93(47.2)	115(49.8)	108(45.6)
Age (months), Mean(SD)	15.8(5.3)	15.3(5.5)	42.4(11.4)	44.2(12.1)
Mother alive, n(%)	203(95.1)	190(99.0)	223(98.2)	229(99.1)
Father alive, n(%)	200(99.5)	190(100.0)	221(98.2)	227(98.3)
Mother's main income from farming own land, n(%)	153(75.0)	150(77.3)	159(68.9)	171(73.1)
Nutrition parameters (all)				
Mid-Upper Arm Circumference (cm), Mean(SD)	10.9(0.8)	10.9(1.0)	11.5(1.0)	11.3(0.9)
Weight (kg), Mean (SD)	6.2(1.1)	6.3(1.2)	8.8(1.6)	8.6(1.6)
Length/Height (cm), Mean(SD)	67.2(5.0)	67.2(5.2)	80.2(7.8)	80.1(7.5)
Bilateral pitting edema, n(%)	26(12.5)	26(13.2)	69(29.9)	57(24.0)
Weight-for-age Z-score, Mean(SD)	-4.0(1.0)	-3.9(1.2)	-4.2(1.0)	-4.4(0.9)
Height-for-age Z-score, Mean(SD)	-4.3(1.5)	-4.0(1.6)	-4.8(1.4)	-5.0(1.4)
Weight-for-height Z-score, Mean(SD)	-2.4(1.1)	-2.4(1.2)	-2.2(1.3)	-2.4(1.3)
Nutrition parameters (children without edema)	n=180	n=170	n=162	n=180
Mid-Upper Arm Circumference (cm), Mean(SD)	10.8(0.6)	10.8(0.8)	11.1(0.5)	11.1(0.4)
Weight (kg), Mean (SD)	6.1(1.0)	6.1(1.1)	8.5(1.4)	8.5(1.3)
Length/Height (cm), Mean(SD)	66.7(4.7)	66.6(5.0)	79.9(7.9)	79.9(7.7)
Weight-for-age Z-score, Mean(SD)	-4.1(1.0)	-4.0(1.1)	-4.4(0.8)	-4.5(0.9)
Height-for-age Z-score, Mean(SD)	-4.3(1.5)	-4.1(1.7)	-4.9(1.5)	-5.0(1.4)
Weight-for-height Z-score, Mean(SD)	-2.5(1.1)	-2.5(1.1)	-2.5(1.1)	-2.6(1.1)
Nutrition parameters (children with edema)	n=28	n=27	n=69	n=57
Mid-Upper Arm Circumference (cm), Mean(SD)	11.6(1.5)	11.9(1.5)	12.3(1.2)	12.0(1.5)
Weight (kg), Mean (SD)	7.2(1.4)	7.5(1.4)	9.6(1.9)	9.2(2.0)
Length/Height (cm), Mean(SD)	70.5(5.9)	71.1(4.3)	81.1(7.3)	80.9(6.7)
Weight-for-age Z-score, Mean(SD)	-3.4(1.2)	-3.2(1.3)	-3.6(1.1)	-4.1(1.1)
Height-for-age Z-score, Mean(SD)	-3.9(1.7)	-3.7(1.4)	-4.6(1.3)	-4.9(1.2)
Weight-for-height Z-score, Mean(SD)	-1.9(1.3)	-1.7(1.6)	-1.5(1.1)	-1.9(1.1)

[1]SMS-RUTF=Soya-Maize-Sorghum Based Ready-To-Use Therapeutic Food; [2]P-RUTF= Peanut paste based Ready-To-Use Therapeutic Food

Table 4: Comparison of overnight-fasted concentrations of selected amino acids at baseline and at discharge

	Control[1] (A)	SMS-RUTF[2](B)	P-RUTF[3](C)	Comparisons (p-values)[4]		
Amino Acid	Median(IQR[5])	Median(IQR)	Median(IQR)	A versus B	A versus C	B versus C
Admission	n=25	n=30	n=30			
Lysine (µmol/l)	102.81(87.49, 142.21)	70.59(44.08, 102.99)	81.80(43.92, 112.06)	0.004	0.009	0.496
Valine (µmol/l)	124.51(103.47 , 161.08)	90.89(57.23, 113.46)	103.91(75.59, 125.41)	<0.001	0.008	0.117
Methionine (µmol/l)	16.54(13.27, 20.30)	10.99(7.22, 15.27)	12.83(10.18, 15.05)	<0.001	0.004	0.178
Cystine (µmol/l)	25.62(20.73, 28.58)	10.48(6.49, 16.98)	16.32(9.08, 21.29)	<0.001	<0.001	0.158
Tyrosine (µmol/l)	45.61(41.60, 52.92)	22.35(11.45, 34.81)	30.36(22.13, 41.68)	<0.001	<0.001	0.209
Tryptophan (µmol/l)	15.41(7.66, 19.20)	4.27(2.50, 9.28)	4.14(2.23, 9.62)	<0.001	0.003	0.685
Phenylalanine (µmol/l)	47.22(41.21, 58.15)	37.67(25.68, 52.43)	39.94(29.34, 55.24)	0.030	0.063	0.469
Discharge	n=25	n=20	n=26			
Lysine (µmol/l)	102.81(87.49, 142.21)	109.22(85.67, 144.31)	99.44(84.81, 144.84)	0.819	0.880	0.690
Valine (µmol/l)	124.51(103.47, 161.08)	117.50(98.27, 139.60)	127.08(103.98, 159.80)	0.385	0.985	0.506
Methionine (µmol/l)	16.54(13.27, 20.30)	13.61(10.48, 15.01)	14.56(11.97, 16.28)	0.005	0.048	0.268
Cystine (µmol/l)	25.62(20.73, 28.58)	24.96(16.70, 34.08)	35.60(29.00, 39.04)	0.715	<0.001	0.004
Tyrosine (µmol/l)	45.61(41.60, 52.92)	39.07(30.36, 54.77)	48.00(41.54, 71.04)	0.537	0.258	0.092
Tryptophan (µmol/l)	15.41(7.66, 19.20)	13.24(8.26, 20.68)	20.13(13.15, 31.61)	0.784	0.024	0.092
Phenylalanine (µmol/l)	47.22(41.21, 58.15)	39.72(33.29, 54.74)	43.57(38.75, 66.60)	0.144	0.638	0.215

Summary statistics are median and interquartile range;[1]Community controls were surveyed only once and the same data is used for comparison with admission and discharge data; [2]SMS-RUTF, Soya-Maize-Sorghum Based Ready-To-Use Therapeutic Food; [3]P-RUTF, Peanut based Ready-To-Use Therapeutic Food; [4]Mann-Whitney test with Bonferroni correction (difference statistical significant if p<0.017); [5]IQR, interquartile range

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Table 5: Between group comparison at discharge and with community controls of body composition parameters measured by deuterium dilution technique

Variables	Control[3] (A) Mean±SD	SMS-RUTF[4] (B) Mean±SD	P-RUTF[5] (C) Mean±SD	Comparison[6] B versus A Difference (95%CI[7])	p-value	Comparison[6] C versus A Difference (95%CI)	p-value	Comparison[6] B versus C Difference (95%CI)	p-value
n	47	29	26						
Age (months)	36.53±18.7	40.75±17.7	33.6±19.0	4.2(-4.4, 12.8)	0.332	-2.9(-12.0, 6.3)	0.534	7.1(-2.8, 17.0)	0.158
Weight (kg)	11.5±2.5	10±2.1	9.2±2.3	-1.5(-2.6,-0.4)	0.010	-2.3(-3.5, -1.1)	<0.001	0.8(-0.4, 2.0)	0.174
Height (cm)	84.5±9.8	79.5±8.6	77.1±9.8	-5.0(-9.7,-0.4)	0.033	-7.5(-12.5,-2.5)	0.004	2.4(-2.5, 7.4)	0.321
MUAC[1] (cm)	14.3±1.2	13.3±0.8	13.1'±0.7	-1.0(-1.4, -0.4)	<0.001	-1.1(-1.6, -0.6)	<0.001	0.2(-0.2, 0.6)	0.260
WAZ[2]	-1.47±0.94	-3.06±0.79	-3.02±0.94	-1.59(-2.03, -1.15)	<0.001	-1.54(-2.02, -1.07)	<0.001	-0.05(-0.51, 0.42)	0.842
HAZ[2]	-2.54±1.48	-4.56±085	-4.12±1.45	-2.02(-2.58, -1.45)	<0.001	-1.59(-2.27, -0.90)	<0.001	-0.44(-1.07, 0.20)	0.177
WHZ[2]	0.02±0.86	-0.44±0.97	-0.77±0.69	-0.46(-0.88, -0.04)	0.033	-0.79(-1.18, -0.40)	<0.001	0.33(-0.13, 0.79)	0.157
Fat Free mass (kg)	9.4±2.6	8.1±2.2	7.6±1.8	-1.3(-2.4, -0.1)	0.034	-1.8(-2.9, -0.6)	0.003	0.5(-0.6, 1.6)	0.341
Body Fat mass (kg)	2.1±1.0	1.9±0.9	1.6±0.9	-0.2(-0.7, 0.2)	0.374	-0.5(-1.0, -0.0)	0.041	0.3(-0.2, 0.8)	0.245
Percentage fat (%)	19.2±9.2	19.7±9.3	17.3±7.3	0.5(-3.9, 4.8)	0.825	-1.9(-6.1, 2.3)	0.369	2.4(-2.2, -7.0)	0.300
Fat Free mass index[8] (kg/m^2)	12.9±1.1	12.7±1.7	12.6±1.1	-0.2(-0.8, 0.4)	0.535	-0.3(-0.8, 0.2)	0.274	0.1(-0.7, 0.9)	0.802
Fat mass index[9] (kg/m^2)	3.1±1.0	3.1±1.5	2.7±1.0	0.0(-0.6, 0.6)	0.999	-0.4(-0.9, 0.1)	0.111	0.4(-0.3, 1.1)	0.262

Summary statistics are means and standard deviation;[1]MUAC, Mid-Upper Arm Circumference; [2]Anthropometric indice weight-for-age Z-score (WAZ), height-for-age Z-score (HAZ) and Weight-for-height Z-score (WHZ); [3]Control (A) are non-wasted children with no history of severe acute malnutrition recruited to serve as community controls; [4]SMS-RUTF (B), Soya-Maize-Sorghum ready-to-use therapeutic food group; [5]P-RUTF(C), standard peanut and milk based ready-to-use therapeutic food group; [6]t-test analysis with Bonferroni correction (difference statistical significant if p<0.017); [7]CI, confidence interval; [8]Fat Free mass index, Fat Free mass relative to height obtained by dividing the Fat Free mass (in kg) to the height (in m); [9]Fat mass index, Body fat mass relative to height obtained by dividing the body fat mass (in kg) to the height (in m).

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Table 6: Between group comparison of bio-electrical impedance analysis parameters of children at time of discharge from therapeutic feeding program

Parameter	SMS-RUTF[1] Mean±SD	P-RUTF[2] Mean±SD	Difference[3] estimate (95% CI[4])	p-value
	n=73	n=90		
At admission				
Age (month)	43.85 ±11.74	42.38 ±13.67	1.47 (-2.52, 5.46)	0.468
Weight(kg)	9.12 ±1.48	8.69 ±1.50	0.43 (-0.04, 0.89)	0.071
Height (cm)	81.69 ±7.52	79.76 ±7.33	1.93 (-0.37, 4.24)	0.1
MUAC[5] (cm)	11.7 ±0.8	11.5 ±0.8	0.2 (-0.0, 0.5)	0.057
At discharge				
Age (month)	45.94 ±11.91	45.30 ±14.97	0.64 (-3.62, 4.90)	0.767
Weight(kg)	10.43 ±1.53	10.46 ±1.1.69	-0.03 (-0.53, 0.47)	0.902
Height (cm)	82.41 ±7.40	80.55 ±7.28	1.86 (-0.41, 4.13)	0.109
MUAC[5] (cm)	13.4 ±0.7	13.6 ±0.8	-0.2 (-0.4. 0.0)	0.094
Fat Free Mass (kg)	8.50 ±1.21	8.58 ±1.11	-0.08 (-0.44, 0.29)	0.661
Fat Mass (kg)	1.93 ±0.81	1.88 ±0.78	0.05 (-0.21, 0.29)	0.69
Percentage Fat Mass (%)	17.6±6.0	18.0±6.0	-0.4(-2.27, 1.47)	0.672
Fat Free Mass Index[6] (Kg/m2)	12.7 ±1.1	13.2 ±1.1	-0.5 (-0.85, -0.15)	0.006
Fat Mass Index[7] (Kg/m2)	2.74 ±1.03	2.96 ±1.17	-0.22 (-0.56, 0.13)	0.21
Phase angle (degree)	3.47 ±0.51	3.74 ±0.53	-0.26 (-0.43, -0.10)	0.002
Resistance (Ohms)	959 ±91	923 ±95	35 (7, 65)	0.016
Reactance (Ohms)	57.92 ±10.32	60.33 ±10.23	-2.41 (-5.60, 0.79)	0.138
Illness marker	0.957 ±0.007	0.95 ±0.013	0.006 (0.003, 0.009)	<0.001
Resistance/Height (Ohm/cm)	1172 ±151	1156 ±166	15.66 (- 34.98, 65.31)	0.534
Reactance/Height (Ohm/cm)	70.47 ±12.25	75.45 ±14.42	-4.99 (-9.18, -0.79)	0.02

Summary statistics are means and standard deviation (SD); [1]SMS-RUTF (B), Soya-Maize-Sorghum Ready-to-Use Therapeutic Food group; [2]P-RUTF(C), Peanut based Ready-to-Use Therapeutic Food group; [3]t-test analysis; [4]CI, confidence interval; [5]MUAC, Mid-Upper Arm Circumference; [6]Fat Free mass index, Fat Free mass relative to height obtained by dividing the Fat Free mass (in kg) to the height (in m); [7]Fat mass index, Body fat mass relative to height obtained by dividing the body fat mass (in kg) to the height (in m).

Figures' legends

Figure 1: study participants flow diagram

ITT, Intention-to-Treat; LOS, Length of Stay; PP, Per Protocol; RUTF, Ready-to-Use Therapeutic Food; P-RUTF, Peanut based Ready-to-Use Therapeutic Food; SMS-RUTF, Soya-Maize-Sorghum Ready-to-Use Therapeutic Food

Figure 2: Intention-To-Treat analysis: difference in recovery rate between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food and Peanut based Ready-to-Use Therapeutic Food for both age groups

Comparison of the difference in estimated marginal means and their bootstrapped 95% CI, The n indicate the total n for the RUTF group, the n for children 6-23 months and the n for children 24 to 59 months;

Figure 3: Per Protocol analysis: difference in recovery rate between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food and Peanut based Ready-to-Use Therapeutic Food for both age groups

Comparison of the difference in estimated marginal means and their bootstrapped 95% CI; The n indicate the total n for the RUTF group, the n for children 6-23 months and the n for children 24 to 59 months

Figure 4: Per protocol analysis: difference in daily weight gain between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food and Peanut based Ready-to-Use Therapeutic Food for both age groups

Comparison of the difference in estimated marginal means and their bootstrapped 95% CI; The n indicate the total n for the RUTF group, the n for children 6-23 months and the n for children 24 to 59 months

Figure 5: difference in length of stay between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food and Peanut based Ready-to-Use Therapeutic Food for both age groups in intention-to-treat analysis and for the recovered children

Comparison of the difference in estimated marginal means and their bootstrapped 95% CI; The n indicate the total n for the RUTF group, the n for children 6-23 months and the n for children 24 to 59 months

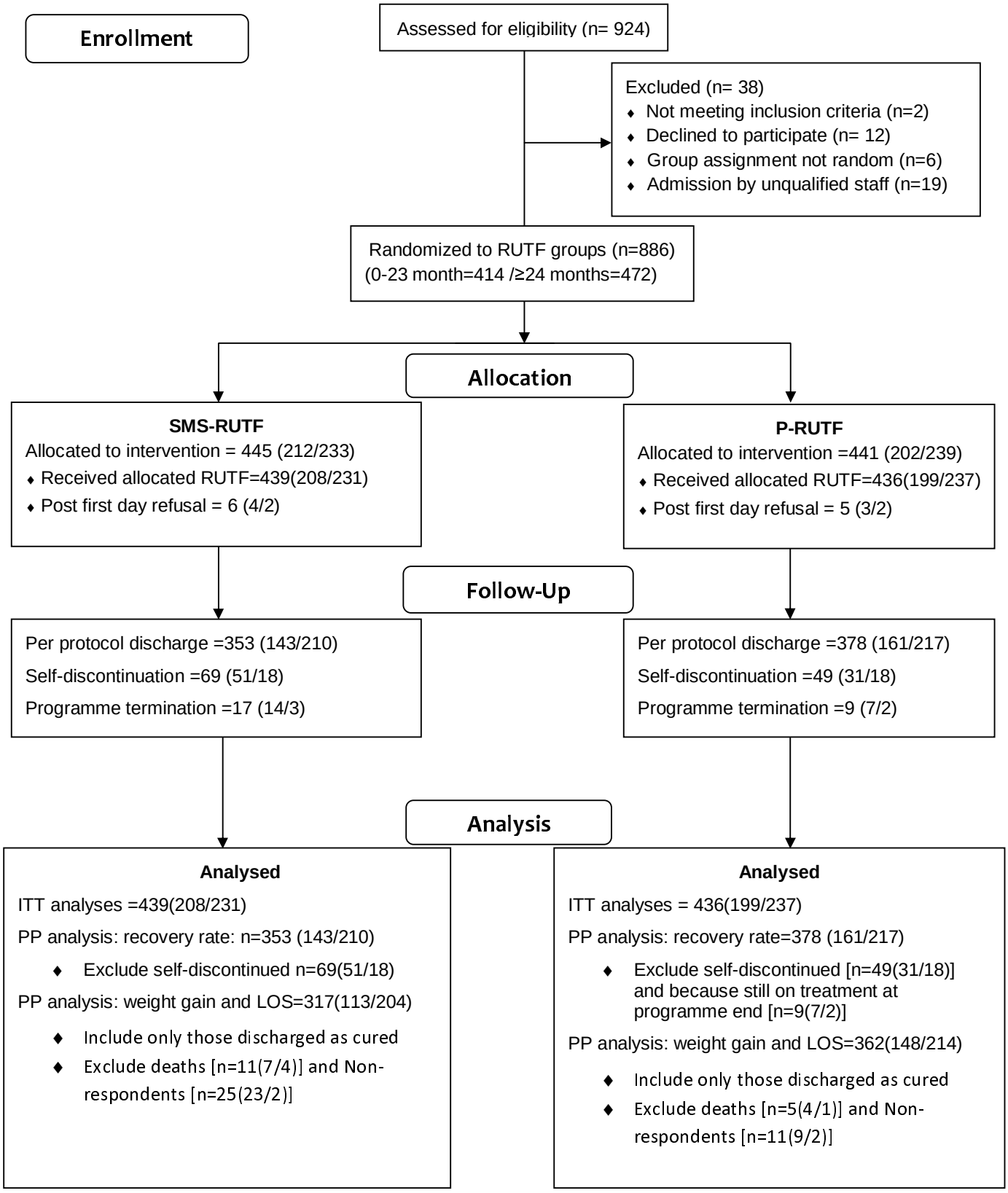

Figure 1: study participants flow diagram

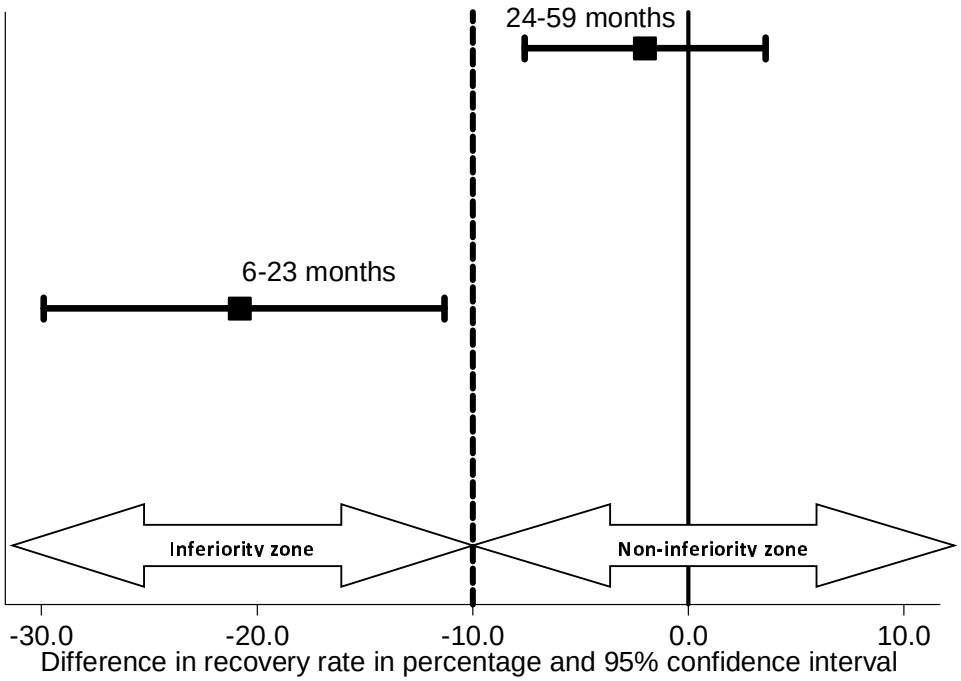

Figure 2: Intention-To-Treat analysis: difference in recovery rate between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food [n=439(208/231)] and Peanut based Ready-to-Use Therapeutic Food [n=436(199/237)] for both age groups

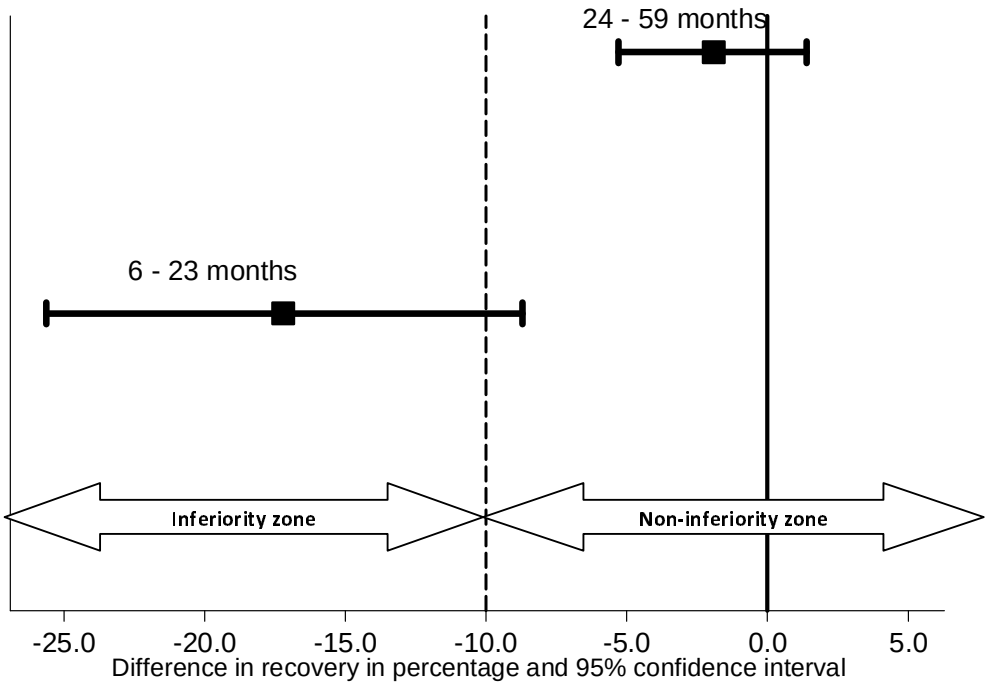

Figure 3: Per Protocol analysis: difference in recovery rate between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food [n=353(143/210)] and Peanut based Ready-to-Use Therapeutic Food [n=378(161/217)] for both age groups

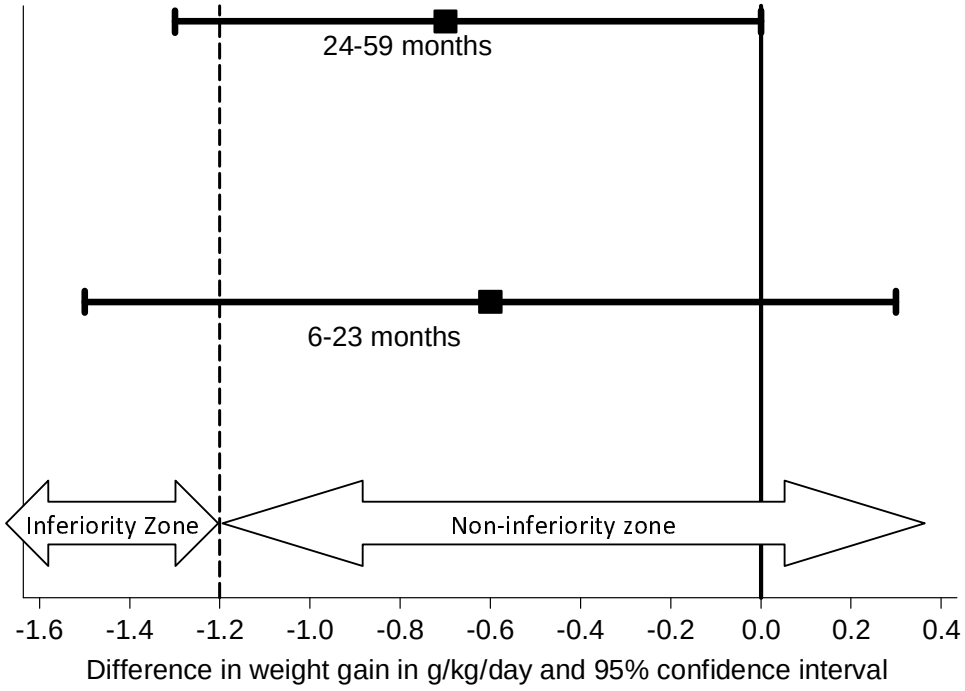

Figure 4: Per protocol analysis: difference in daily weight gain between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food [n=317(113/204)] and Peanut based Ready-to-Use Therapeutic Food [n=362(148/214)] for both age groups

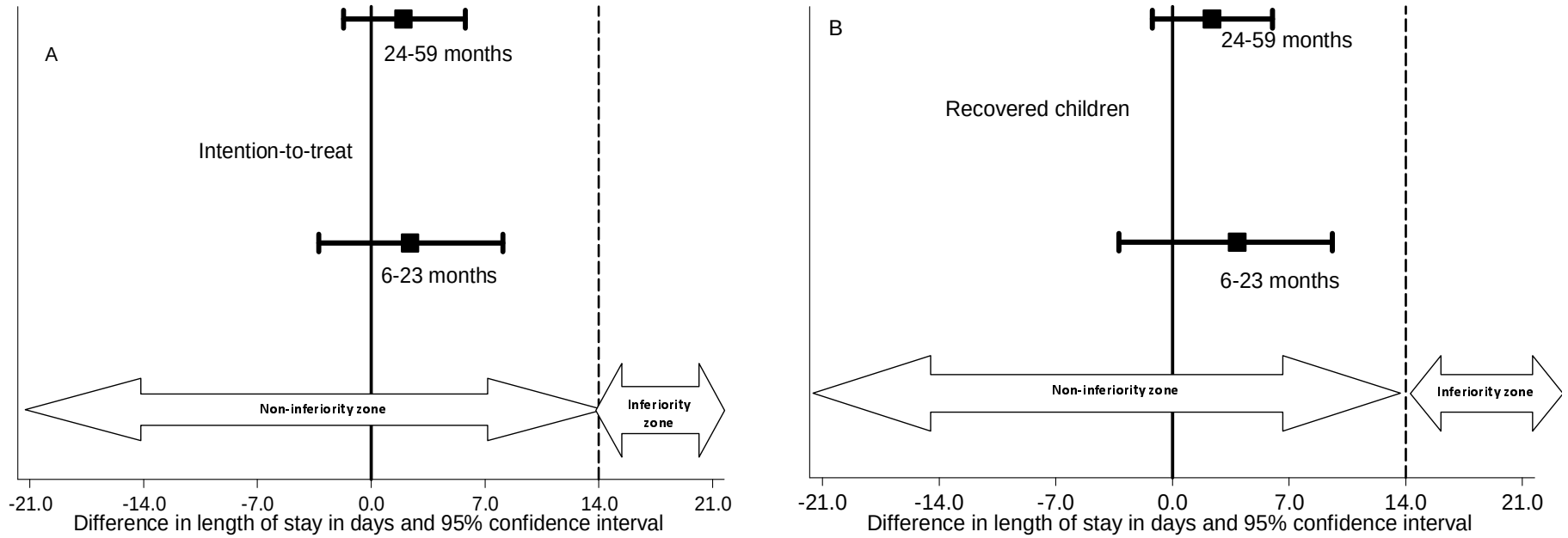

Figure 5: difference in length of stay between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food [n=439(208/231)] and Peanut based Ready-to-Use Therapeutic Food [n=436(199/237)] for both age groups in intention-to-treat analysis (A) and difference between recovered children (B) of the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food group [n=317(113/204)] and Peanut based Ready-to-Use Therapeutic Food [n=362(148/214)]