The American Journal of Clinical Nutrition
AJCN/2015/119537
Version 2
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

Corresponding Author: Paluku Bahwere
Additional Authors: Bisimwa Ghislain Balaluka, Jonathan C Wells, Cobohwa Nickel Mbiribindi, Kate Sadler, Peter Akomo, Michele Dramaix-Wilmet, Steve Collins

This paper includes additional materials for review purposes. To view additional materials, click on the [Download Supplemental Files] link available in the Full MS Info view of the manuscript. To reach this manuscript view, go to http://submit.ajcn.org , and log in to your account. Enter the Reviewer Area and click on Active Reviews.

Information for Authors: http://www.ajcn.org/site/misc/ifa.xhtml

Title page

Title: **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**

Authors names:

Paluku Bahwere, Bisimwa Balaluka, Jonathan C. K. Wells, Chobohwa N. Mbiribindi, Kate Sadler, Peter Akomo, Michèle Dramaix-Wilmet, Steve Collins

Authors affiliations:

1. Valid International, 35 Leopold Street, Oxford OX4 1TW, UK (PB, KS, SC)

2. Centre de Recherche en Epidémiologie, Biostatistique et Recherche Clinique, Ecole

de santé publique, Université Libre de Bruxelles, Belgium (PB, MD).

3. Centre de Recherche en Sciences Naturelles de Lwiro, Sud-Kivu, Democratic Republic of Congo (BB, CNM)

3. College of Medicine, Catholic University of Bukavu, South-Kivu, Democratic Republic of Congo (BB)

4. Childhood Nutrition Research Centre, UCL Institute of Child Health, London, UK (JCKW)

5. Valid Nutrition, Cuibín Farm, Derry Duff, Bantry, Co., Cork, Republic of Ireland (PA)

Authors last names:

Bahwere, Balaluka, Wells, Mbiribindi, Sadler, Akomo, Dramaix-Wilmet, Collins.

Corresponding author:

Paluku Bahwere, Valid International, 35 Leopold Street, Oxford OX4 1TW, UK. E-mail:

paluku@validinternational.org; Tel: +44 (0)1865 722180

Reprints request to:

Paluku Bahwere, Valid International, 35 Leopold Street, Oxford OX4 1TW, UK. E-mail:

paluku@validinternational.org

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; **Ph**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

1   **Abstract**

2   **Background:** The cost of current standard Ready-to-Use Therapeutic Food (RUTF) is

3   among major obstacles to the scale up of Community-based Management of Acute

4   Malnutrition (CMAM), an important child survival strategy. Identifying a cheaper

5   alternative is a global public health priority.

6   **Objective:** We compare the efficacy of Soya-Maize-Sorghum RUTF (SMS-RUTF) with that

7   of standard RUTF (P-RUTF).

8   **Design:** This was a non-blinded, parallel group, simple randomised, controlled trial that

9   enrolled two groups of SAM children (6 and 23 months and 24 – 59 months) and used a

10 day care approach.

11 **Results:** Intention-to-treat (ITT) and per protocol (PP) analyses showed non-inferiority

12 of SMS-RUTF compared to P-RUTF for recovery rate [Δ =-2.0%(95%CI -7.6, 3.6) in ITT

13 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

14 Length of stay [Δ=2.0(95% CI, −1.7, 5.8)days] in children ≥24months. In children ≤23

15 months, recovery rate with SMS-RUTF was inferior to that with P-RUTF [Δ=-20.8%

16 (95%CI -29.9, -11.7) in ITT and -17.2%(95%CI −25.6, -8.7) in PP].   Treatment with SMS-

17 RUTF resulted in a greater increase in hemoglobin [0.670(0.420, 0.921)g dl-1; p<0.001].

18 Treatment with both RUTFs resulted in the replenishment of all the amino acids tested,

19 except for methionine. There were no differences at discharge between RUTF groups in

20 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)

21 kg m^{-2}; p=0.262]. By contrast, comparisons of fat free mass indicated lower levels of FFM

22 than the community controls after treatment with either of the two RUTFs [Δ=-

23 1.3(95%CI −2.4, -0.1)kg; p=0.034 for comparison between community controls and the

24 SMS-RUTF group and Δ=-1.8(95%CI −2.9, -0.6)kg; p=0.003 for comparison between

25 community controls and the P-RUTF group].

26   **Conclusion**: SMS-RUTF can be used to treat SAM in children ≥24 months of age to

27   reduce the costs of CMAM programmes.   More research is required to optimize SMS-

28   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

55   ambient temperatures and used in poor communities (5). The most widely used RUTF

56   referred as P-RUTF in this paper, is a mixture of milk powder, sugar, vegetable oil, peanut

57   butter, vitamins, and minerals(5;6). It is equivalent to the WHO F-100 milk(7). This RUTF

58   recipe has been used widely in CMAM to treat severely malnourished children in resource-

59   poor settings(8) with demonstrably high recovery rates, low case-fatalities, and greater weight

60   gain has been demonstrated using P-RUTF(2;9;10). However, the high milk content of this

61   formulation makes it very expensive for sustainable use in resource-poor settings and

62   increases the proportion of ingredients that have to be imported into developing countries.

63

64   To lower the cost and increase the potential for using locally grown ingredients, Valid

65   Nutrition has developed a new milk-and peanut free recipe based on locally produced crops.

66   This recipe is made from Soya, Maize and Sorghum (SMS-RUTF), and may provide a

67   cheaper alternative to the P-RUTF currently used. However, the efficacy of this formulation

68   compared to P-RUTF has not been formally demonstrated. An initial study assessing the

69   effectiveness of SMS-RUTF in Lusaka yielded inconclusive results with the recovery rates in

70   both the intervention and the standard group below international SPHERE standard and an

71   unexplained high level of mortality(11). Likely explanations of the inconclusive results

72   included the cholera and measles epidemics and floods that occurred during the study period

73   causing abnormal increases in mortality and default rates(11). Despite these inconclusive

74   results, lessons learned from that trial have been used to improve both the composition of the

75   SMS-RUTF and the design of studies used to evaluate it.

76

77   The study reported here examined the efficacy of SMS-RUTF compared to P-RUTF using a

78   design and context that minimized operational constraints. The SMS-RUTF product used had

79   an enhanced phytic acid and iron and phytic acid and zinc molar ratios and improved omega-

80   6 amega-3 fatty acid profile ratio (11) compared to the product tested in Lusaka. The study

81   also included a comparison of changes in hemoglobin, amino acid profile and body

82   composition during recovery in addition to the standard outcome indicators of recovery rate,

83   weight gain and length of stay. The hypotheses assumed are that SMS-RUTF is not inferior to

84   P-RUTF for recovery rate, weight gain and LOS and that treatment with SMS-RUTF will be

85   associated with higher hemoglobin increase.

86 **Methods**

87 **Study design**

88 ***Primary objectives***

89 This was a non-blinded, parallel group, simple randomized, controlled trial to compare the

90 efficacy of SMS-RUTF with that on P-RUTF in the treatment of SAM in two groups of

91 children, those aged between 6 and 23 months and those aged between 24 – 59 months. The

92 non-inferiority hypothesis was chosen because the overall aim of the research was to develop

93 a RUTF as effective as the highly effective standard RUTF but cheaper and was assumed

94 based on the result of a previous study into SMS-RUTF undertaken by this team in Lusaka,

95 Zambia(11). Differences in the color and taste between the SMS-RUTF and the P-RUTF

96 precluded blinding the study. To ensure that the research team had full control over all

97 treatment parameters and could collect daily data on morbidity, a day care approach was used,

98 wherein study subjects attended an outpatient treatment center for 8 hours each day to receive

99 standardized treatment protocols. This day-care approach eliminated the risks that subjects

100 shared or sold the RUTF and the risk that the energy and micronutrient densities of the RUTF

101 was altered by inappropriate mixing with other food. The day care approach also helped

102 improve the assessment of the adherence to the study protocol and accurately quantifying

103 individual daily intakes of RUTF.

104 ***Secondary objectives***

105 The study also compared changes in hemoglobin, the replenishment of amino stores and

106 changes in body composition attributable to the two products. Hemoglobin was measured at

107 admission and at discharge from the study and in a sub-sample of participants selected

108 randomly throughout the study period. The replenishment of amino-acid stores was assessed

109 by measuring plasma level of the free amino acids (lysine, valine, tryptophan, tyrosine,

110   phenylalanine, methionine and cysteine) in overnight-fasted malnourished children before

111   starting nutrition rehabilitation, upon discharge from the study and in age / sex matched non-

112   wasted community controls recruited from the same area as the malnourished participants.

113   Body composition was assessed using two techniques. Deuterium Dilution Technique (DDT)

114   was used to assess Total Body Water (TBW), Fat Free Mass (FFM) and Body Fat Mass (FM).

115   This sub-study used the change in the concentration of deuterium in samples of saliva after an

116   intake of a standardized oral dose of Deuterium oxide to estimate TBW and FM and FFM and

117   derived indexes. It was conducted in a sub-sample of study subjects at discharge and

118   compared to the levels found in age and sex matched non-wasted community controls.

119   Bioelectrical Impedance Analysis (BIA) was used to also estimate TBW, FM, FFM, and

120   derived indexes. Other specific BIA parameters of Reactance and Resistance (Phase angle,

121   Wellness Marker), were also measured. These were assessed using a dual frequency portable

122   Bodystat 1500MDD in another randomly selected sub-sample of children aged 24 - 59

123   months drawn from each of the treatment groups. These children were assessed at the

124   beginning of nutrition rehabilitation, then again when their MUAC reached 12.5cm and again

125   at exit from the study.

126   **Setting**

127   The study was undertaken in Miti-Murhesa Health Zone (HZ) located in the Kabare

128   administrative zone of South Kivu province in Democratic Republic of Congo. The HZ

129   covers an area of 525 km^2 adjacent to Lake Kivu and consists of highland plains and hills at

130   elevations ranging between 900–1900m. It has a tropical highland climate. At the last census

131   in 2011, it had a recorded population of 204,368 with a very high population density of 392

132   inhabitants per km^2. The main economic activities are subsistence agriculture and small scale

133   trading. In 2011 the HZ had 40,000 children aged 6 to 59 months with a prevalence of SAM

134   in these children of 2.2%(12). Breastfeeding is universal but the prevalence of exclusive

135   breastfeeding until 6 months is low with the average duration being 2.5 months (13;14). The

136   diet of infant and young children has remained unchanged for decades and is poor in diary

137   and other animal source foods(15). The HZ has 16 health centers (HCs) and 4 hospitals and

138   before the study started was running a limited CMAM program with 3 outpatient sites for the

139   management of uncomplicated SAM and one stabilization center for the management of SAM

140   with complications. The geographical coverage of this program and the number of

141   admissions were however very low and between May - August 2011 only 40 SAM children

142   were admitted into the CMAM program out of a predicted case load of over 800. This study

143   was implemented in 10 out the 16 HCs and used one of the hospitals as a referral center for

144   the stabilization of SAM with complications.

145   **Study populations**

146   The study participants were selected from children admitted into the government run CMAM

147   program in Miti-Murhesa HZ. The government CMAM program admitted all children aged

148   between 6 and 59 months diagnosed with SAM (mid upper arm circumference [MUAC]

149   <115mm or bilateral pitting edema of any degree). Length or height was measured but the

150   related nutrition indices were not used either in decision to admit or discharge children or in

151   in the definition of outcome. Children with MUAC < 115mm and good appetite and no

152   medical complication and those with bilateral pitting edema assessed as + or ++ who also had

153   good appetite and no medical complication were admitted directly into the day-care

154   component of the study program. Those with bilateral pitting edema assessed as +++ degree

155   or with any medical complication at enrolment were referred to the participating inpatient

156   facility where they received inpatient care until stabilized, after which time they were

157   admitted into the day-care study program. Children with any medical or nutritional

158   complication during follow up were also referred to the participating inpatient facility for

159   appropriate treatment of the complication, after which they were re-admitted into the day-care

160   program and remained in their original study group. Medical complications were defined

161   using the World Health Organization's CMAM and Integrated Management of Childhood

162   Illness (IMCI) standard definitions (2;16). Nutrition rehabilitation during inpatient followed

163   the national guidelines and therapeutic milks F75 and F100 were used as appropriate.

164

165   Study subjects were admitted into the study at the same time as they were admitted into the

166   day care phase of the study program. Great attention was given to avoid the admission into

167   the study of any children who were not suffering from SAM and before inclusion in the study,

168   all potential subjects were re-examined by senior supervisors (all of whom had over 10 years

169   experience in the diagnosis and management of SAM) to confirm that the diagnosis of SAM

170   was correct. The presence of edema, the most difficult to assess diagnostic criteria for SAM,

171   was confirmed by the senior supervisor prior to enrolment into the study. Children admitted

172   into the CMAM program for whom senior supervisors did not confirm presence of edema

173   were excluded from the study. Children with congenital or acquired disorders affecting

174   growth, any history of any food allergy, a history of treatment for SAM in the previous 3

175   months and those from visiting families were also excluded.

176

177   The community control groups for the body composition and amino acid studies were

178   recruited from the same neighborhoods as the malnourished children included in the main

179   study. These controls were matched for the age at enrolment (± 1 month) and the gender of

180   the malnourished child. Technical difficulties in conducting the BIA assessments in children

181   younger than 24 months meant that only children aged 24 - 59 months and above were

182   eligible for inclusion in the BIA component.

Randomization

184   The study used simple randomization (ratio 1:1). After confirming eligibility for inclusion in

185   the study, children were randomized by a closed envelope method to receive either SMS-

186   RUTF or P-RUTF. A computer-generated sequentially numbered randomization list (with

187   variable block sizes) that contained both allocations and codes for 900 children was pre-

188   prepared by the trial statistician who was based outside the DRC. These were sent to the

189   national study coordinator who then prepared 900 opaque, sealed, and consecutively

190   numbered randomization envelops. A block of 20 envelopes were distributed to the

191   enumerator team leaders at each study site who used them to allocate a "Study Group" to each

192   subject at admission. The team involved in the assessment of the child for eligibility and in

193   their follow up had no role in the allocation of the Study Group.

Monitoring and follow up

195   The study was conducted in specially built "study day care sites" erected at each of the

196   participating health centers (HCs). After enrolment, caregivers were asked to bring the

197   children to nearest site every day between 8am – 4pm until discharged and the mother or

198   another family member had to stay with the child. At each site, a minimum of two HC nurses

199   and one field nutritionist monitored the children's clinical and nutrition parameters, including

200   checking the progress of nutritional recovery and identifying and treating any concurrent

201   infection. At each site, two study assistant nurses fed the children with the support of the

202   caregivers. Children were not allowed to take RUTF home and caregivers were advised not to

203   feed children in the morning before coming to the site, except for children still on breast milk.

204   No special recommendation was given for evening meal. Each study nurse assistant had less

205   than 10 children to feed. The study nurse assistants were allocated to one study group for half

206   of the study period before being changed to the other study group for the other half of the

207   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

233   signs of disease, laboratory results at admission and during nutrition rehabilitation, nutrition,

234   clinical signs and type of discharge. The nurses collected the data every morning during the

235   period of study participation. A specially designed questionnaire book was used by study

236   assistant nurses to collect additional information including actual RUTF intake, symptoms

237   and physical signs of diseases observed by them during their surveillance of children at the

238   feeding site and symptoms such as bloating, flatulence, abdominal pain or diarrhea that could

239   have been related to RUTF intake. Special forms were designed and used for the collection of

240   specific data for BIA parameters and saliva samples for body composition assessment and

241   blood samples for amino acid assessment.

242

243   A trial week of the implementation of all protocols and routine data collection procedures

244   preceded the start of the study in order to ensure the standardization of data collection and

245   iron out any initial problems.

246   **Procedures**

247   Weight, height or length and MUAC were measured following WHO recommended

248   procedures (18). Hemoglobin concentrations were measured in capillary blood, obtained from

249   the fingertip, using a portable Hemoglobinometer (HemoCue® AB, Ängelholm, Sweden).

250   The device was calibrated on a daily basis using a HemoCue Control Cuvette. BIA

251   parameters were determined using the manufacturer-recommended procedures for the hand-

252   foot Bodystat 1500 MDD system (Bodystat Inc, Douglas, United Kingdom), with

253   accompanying measurements of weight and height. BIA was measured with the child in

254   supine position with arms and legs slightly abducted from the trunk. The measurement started

255   after 3 to 4 minutes in that position and was done with electrodes placed at the dorsal surfaces

256   on wrist (between second and third metacarpals) and ankle (between second and third

257   metatarsals) with the proximal and distal electrodes placed at a minimum of 5cm apart. The

258   impedance was measured at the frequencies of 50 KHz. The deuterium dilution technique

259   (DDT) was undertaken in well-hydrated children with empty bladders. Children were

260   considered well-hydrated if they had no history of diarrhea for the past week, had no history

261   of strenuous activity in the past 3 hours, had wet mouth and no history of recent sunken eyes

262   and had no clinically noticeable edema. A single 3g dose of deuterium (children <10kg) or 6g

263   (children 10 to 20 kg) was given in the morning after an overnight fast. The deuterium dose

264   was pre-weighed on an electronic scale accurate to 0.01 g. Saliva samples were collected

265   before the deuterium dose (baseline sample), 3 hours post ingestion (post-dose sample 1) and

266   4 hours post ingestion (post-dose sample 2). The children were instructed to refrain from any

267   food or fluid for at least 30 min before the post-dose saliva samples. Saliva was collected by

268   getting the children to chew on a ball of cotton wool to fill the ball with saliva. The saliva

269   was then sucked up out of the ball by a syringe. A sample collection was deemed successful if

270   at least 2ml of saliva was collected. After collection, saliva samples were stored in a cool box

271   for not more than 6 hours before being transferred to a freezer where they were stored at –

272   20ºC until shipment to the Nairobi based Kenya Medical Research Institute laboratory where

273   they were also kept frozen until analysis. The deuterium enrichment in the saliva samples was

274   measured by Fourier Transform Infared (FTIR) spectrometry(19). In the Deuterium Dilution

275   technique, TBW was calculated using the value of the deuterium enrichment of the saliva, and

276   the data were analyzed in association with the weight and height measured on the day of

277   dosing. In the BIA analysis, TBW was calculated using a predictive equation developed using

278   anthropometric data and BIA parameters collected in Ethiopian infants and children by one of

279   the authors (20). This equation was deemed by the authors to be more appropriate than other

280   published equations. The FFM was derived from TBW derived using published age and

281   gender specific constants for FFM hydration(21). Human Immunodeficiency Virus (HIV)

282   status was determined by Determine® and Unigold® using the serial approach as

283   recommended by the national guidelines. Plasma samples for amino acid analysis were

284   obtained by venipuncture and collected in tubes with EDTA as an anticoagulant. The blood

285   samples were stored immediately into Cubecooler ™ to maintain blood temperature at 4°C to

286   prevent micro-hemolysis and degradation of amino acid by enzymes present in blood cells

287   (22). Samples were transported within 4 hours after collection to a laboratory for

288   centrifugation and deproteinization.   The blood was centrifuged at 3000g for 15 minutes at

289   4°C to separate plasma (supernatant) from blood cells. For deproteinization, 100 µl of plasma

290   were mixed with 200ul of 5% trichloro-acetic acid and the mixture was centrifuged at

291   10,000g for 10min at 4°C. The supernatant obtained from this second centrifugation

292   (deproteinezed plasma) was then stored at−20°C until shipping in bulk to the Ajinomoto

293   laboratory in Japan and was used for plasma amino acid measurement. The amino acid was

294   measured by an L-8900 dedicated automated amino acid analyzer (Hitachi High-

295   Technologies, Tokyo, Japan) composed of a guard column and analytical column, following

296   standard instruction from the device manufacturer (23).

297

Food products used in the study

299   Both study RUTFs were produced in Valid Nutrition factory in Malawi, an officially

300   recognized UNICEF RUTF supplier. The factory has been supplying the Ministry of Health in

301   Malawi since 2005 and has produced study foods for several published studies (11;24-30).

302   Table 1 provides the composition of the two RUTFs obtained using the US Department of

303   Agriculture food composition database, while **table 2** compares their amino acid profiles

304   obtained from actual laboratory analysis of the two products. The two types of RUTF were

305   packed in similar sachets with different colored labels. Based on our experiences from the

306   Lusaka trial, we modified the micronutrient profile of the SMS-RUTF product used in this

307   study, using a specially formulated vitamin and mineral premixes, and used dehulled soybean

308   and degermed maize. The final product met the WHO 2007 recommendations for RUTF

309   mineral and vitamin levels. To compensate for the higher phytic acid (PA) content in the

310   SMS-RUTF and improve the PA/iron and PA/Zinc molar ratio we increased the concentration

311   of iron, zinc in the SMS-RUTF above the WHO recommended concentrations (31;32). To

312   improve Iron bio-availability in the SMS-RUTF we increased the Vitamin C content above

313   the WHO recommendations. We also increased the n-3 polyunsaturated fatty acid (PUFA)

314   content and decreased the n-6 PUFA to obtain a n-6 PUFA: n-3 PUFA ratio less than 5(33).

315

316   A pre-trial panel test demonstrated that the above changes did not affect consistency, color,

317   odor or taste when compared to the product used in the Lusaka trial and we therefore did not

318   re-run acceptability trial on the product. However, to ascertain and compare the acceptability

319   of the two trial products particularly with regard to the difference in iron, lactose and non-

320   digestible oligosaccharides content, during the efficacy trial we collected data on abdominal

321   pain, the occurrence of diarrhea, flatulence, abdominal distension and actual daily intake

322   (34;35).

323   **Outcomes**

324   The primary outcomes of interest for this study were recovery rate, average daily weight gain

325   and average length of stay (LOS). Secondary outcomes included hemoglobin change,

326   difference in, Fat Mass (FM), Body Fat Percentage (%BF) and Fat Mass Index (FMI), Fat

327   Free Mass (FFM) and Fat Free Mass Index (FFMI) Phase Angle (PhA), and Illness Marker

328   [IM]. The Plasma concentrations of 8 key amino acids at discharge were also studied.

329   **Sample size**

330   We calculated the sample size to demonstrate that SMS-RUTF was not inferior to P-RUTF

331   for recovery rate, weight gain and LOS among children with SAM discharged as recovered

332   from the study. The sample sizes were calculated for a power of 80% and a level of statistical

333   significance of 0.05. The margins of non-inferiority were 10% for recovery rate, 1.2 g kg^{-1}

334   day^{-1} for weight gain, and 14 days for LOS. These margins were defined based on the findings

335   of our previous study conducted in Lusaka (11). For the recovery rate, the margin of non-

336   inferiority of 10% is fixed based the Lusaka SMS-RUTF study that suggested a recovery rate

337   of over 80% for the standard treatment (per protocol analysis) and the SPHERE standard

338   requirement of minimum recovery of 75%. Based on data of the SMS-RUTF Lusaka study in

339   which the weight gain rate and the 95% CI for the P-RUTF was 3.3 (2.8-3.7), the margin of

340   non-inferiority was fixed at 1.2g/kg/day. The non-inferiority margin for the length of stay of

341   14 days was fixed based on the cost of the program and the fact that follow ups of these

342   children are either weekly or fortnightly. We estimated that a difference of 14 days will be

343   associated with a significant increase in cost of treatment in a context of restricted budget. As

344   the findings of our earlier study in Lusaka indicated potentially different responses between

345   younger and older children, sample sizes were calculated separately for children 6-23 months

346   of age and for those aged 24 - 59 months (11). The sample size was calculated using the web-

347   based software "Power"(36). A total of 448 SAM children aged 6-24 months and 316 SAM

348   children 24 to 59 months were required to be 80% sure that the lower limit of a one-sided

349   95% confidence interval (CI) would be above the set limits of non-inferiority (37;38). Due to

350   budgetary constraints convenience samples were chosen for the secondary objectives. These

351   were 200 SAM children (100 per study group) and 20 age and sex matched community-

352   controls for hemoglobin; 60 SAM children (30 per study group) and 60 age and sex matched

353   community-controls for body composition by DDT; 200 SAM children (100 per study group)

354   for body composition using BIA and 60 SAM children and 25 age and sex matched controls

355   for the determination of the distribution of free amino acids concentrations.

356 **Data management, definitions and analysis**

357 *Data management*

358 Throughout the study, the data quality manager and the principal investigator conducted field

359 supervisions during which they spot-checked the quality of anthropometric measurements,

360 edema diagnosis, individual data collection forms and the study questionnaire books filling.

361 All the individual data collection forms were checked again for accuracy and completeness at

362 the time of child discharge from the study. The verified forms were then collected for data

363 entry. Data were double entered by two enumerators into a customized Epidata database

364 prepared for this study (39). Quality of data entry was monitored by the supervisors who

365 cross-checked a random selection of 10% the records. Given that independent teams

366 regularly verified anthropometry measurements, no value was excluded. Cleaned data were

367 exported to stata-11 (40) for analysis.

368 *Definitions*

369 Recovery rates were defined as the percentage of children who were discharged as recovered

370 from the study divided by the total number of children who exited the study. The total of

371 children who exited the study included all those who defaulted, died or were discharged as

372 non-recovered after either meeting the non-recovered criteria (90 days in the program) or at

373 the closure of the program. A child was considered to have defaulted if he/she was absent for

374 five consecutive daily visits and if he/she refused to return after two community workers

375 home visits.

376 Rates of weight gain were calculated by dividing the weight gain expressed in grams (weight

377 at exit –weight at admission) by the weight at admission (in kilograms) and the LOS (in

378 days).

379   Average weight gains were measured as the mean of the individual weight gains expressed in

380   g/kg/day. The average LOS was calculated by dividing the sum of individuals LOS by the

381   total number of children included in the numerator calculation.

382   The hemoglobin change was the difference in blood hemoglobin concentrations between

383   admission and discharge from the study in all children with measurements taken at both

384   points.

385   FM in both the Deuterium Dilution Technique and BIA was calculated as the difference

386   between body weight (BW) and FFM. %BF was obtained by the equation

387    $\%BF=(FM*100)/BW$. The FFMI (fat-free mass/height^2) and FMI (fat mass/height^2) were

388   obtained by dividing FFM and FM expressed in kilograms, by the square of the height

389   expressed in meters. Resistance (R) and reactance (Xc) were adjusted for height by dividing

390   the observed values of these BIA parameters by the height of the child (41). PhA and IM were

391   calculated directly by the BIA Bodystat MDD machine.

392   ***Analysis***

393   Means and standard deviations (SD), medians and interquartile ranges (IQR) or proportions

394   and 95% Confidence intervals (95%CI) were used to describe the admission and exit

395   parameters, as appropriate. Means were compared using t-test, medians using the Mantel–

396   Haenszel test and proportions using the Student's chi-squared test. Differences in the

397   estimated marginal mean between the treatment groups along with a bootstrapped 95% CI

398   was estimated to draw inference on non-inferiority.

399   For the primary outcomes, in accordance with recommendations for analyzing and reporting

400   equivalence and non-inferiority studies, both Intention-To-Treat (ITT) and Per-Protocol (PP)

401   analyses were performed and the confidence intervals were used to interpret any differences

402   (42;43). The ITT analyses included all children enrolled in the study. The PP analyses for

403   recovery rates included all children discharged out of the program as recovered, dead or non-

404   recovered but excluded children who defaulted or who transferred out of the program and

405   were lost to follow-up after inpatient transfer. The PP analyses for weight gains included only

406   the children who were discharged as recovered. Logistic regression was used to test for

407   interactions between the recovery rate and other variables. For the secondary outcomes,

408   means were compared using Student's two-tailed *t* test and median were compared using

409   Kruskall-Wallis. Bonferroni correction was applied in case of multiple comparisons of means

410   or medians and level of p-value for reaching statistical significance adjusted accordingly.

411   Multiple linear regression was used to model effect of SMS-RUTF on hemoglobin increase.

Ethical considerations

413   Permission to conduct the study was obtained from the Ethics Committee of the Catholic

414   University of Bukavu (DRC) and the study was registered prior to staring data collection in

415   the Pan African Clinical Trial Registry (PACTR201303000475166). At the time of

416   admission, each child's parent or carer was informed about the nature and purpose of the

417   study and asked for their verbal and written consent for their child to be included and for their

418   medical information to be used for research purposes. When parents or carer withheld consent

419   for participation, children were referred to one of the four non-participating clinics providing

420   care for SAM in Miti-Murhesa HZ. These clinics were supported by the DRC Government

421   and UNICEF. They used Standard P-RUTF procured from France. The other benefit of

422   participating children included free medical care for any episode of disease during the follow

423   up and one porridge meal per day given to carers when looking after their children at the

424   feeding site.

425   A data safety monitoring board was assigned to perform an ongoing review of study outcomes

426   based on data extracted by themselves from either the study subject's files or the study

427   database during the bi-monthly visit. The findings served only to decide if the study should be

428   ended due to an indication of serious side effects. No serious side effects were detected and

429   no reasons for interrupted the study identified.

430

Results

432   Enrolment and movement of subjects from preliminary screening to data analysis for the

433   whole cohort and by age category are shown in **Figure 1**. Between March 2013 and February

434   2014, a total of 924 eligible children were screened, of whom 886 were randomized to either

435   SMS-RUTF (n = 445) or P-RUTF (n = 441) study groups. Thirty-eight eligible children were

436   excluded prior to randomization and another 11 children (6 in the SMS-RUTF group and 5 in

437   the P-RUTF group) withdrew from the study after only one day of attendance after they

438   realized that they could not fulfil the daily attendance requirement. This was classified as

439   "after first day refusal".

440   Baseline characteristics of children included in the ITT analyses for each study group are

441   shown in **table 3**. Marasmus was the dominant form of SAM among children enrolled into

442   the study and there was no significant difference between groups at baseline for the

443   parameters considered in either of the two age categories.

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

445   In children between 24 – 59 months of age the results of the ITT analysis showed that both

446   products met international minimum standards. In the SMS-RUTF group, recovery,

447   mortality, defaulter and non-response rates were 88.3% (204/231), 1.7% (4/231), 7.8%

448   (18/231) and 2.2% (5/231), respectively. In the P-RUTF group the results were 90.3%

449   (214/237), 0.4% (1/237), 7.6% (18/237) and 1.7% (4/237), respectively.

450

451   By contrast, in children 6 - 23 months of age the ITT analysis demonstrated that international

452   minimum standards were met for the P-RUTF group but not for the SMS-RUTF group. In

453   this age category the SMS-RUTF group's recovery, mortality, defaulter and non-response

454   rates were 54.3% (113/208), 3.4% (7/208), 24.5% (51/208) and 17.8%(37/208) compared to

455   75.1% (148/197), 1.0% (2/197), 15.7% (31/197) and 8.1% (16/197) in the P-RUTF group.

456   **Primary outcomes**

457   Both ITT and PP analyses showed that in children aged 24 -59 months the recovery rate

458   (predefine non-inferiority margin $\Delta = 10\%$) of the SMS-RUTF group was not inferior to the

459   recovery rate of the P-RUTF group. By contrast, in children aged 6 - 23 months the recovery

460   rate in the SMS-RUTF group was inferior to the recovery rate in the P-RUTF group (**figures**

461   **2 and 3**). For weight gain, the PP analysis for weight gain in children who were discharged as

462   recovered showed that the SMS-RUTF group was not inferior to P-RUTF group (predefined

463   non-inferiority margin $\Delta = 1.2$ g/kg/day) in either age category (**Figure 4**). SMS-RUTF was

464   not inferior to P-RUTF in terms of LOS (predefined non-inferiority margin of $\Delta = 14$ days)

465   both in ITT analysis and among recovered children (**figure 5**).

466

467   **Results of the secondary outcomes**

468   ***Hemoglobin***

469   The unadjusted analysis showed no difference in the means hemoglobin changes between the

470   two RUTF groups for all children evaluated [+1.04(0.79-1.30) g/dl for SMS-RUTF group

471   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

472   discharged as recovered [+1.23(0.95-1.50) g/dl for SMS-RUTF group versus +1.19(0.90-

473   1.47) g/dl, a difference of 0.04(-0.35, 0.44) g/dl; p=0.837)]. The difference in the proportion

474   of anemic children (hemoglobin<11.0 g/dl) in children discharged as recovered was also not

475   statistically significant [19/72=26.39% for SMS-RUTF group and 24/80=30.0%, a difference

476   of -3.61(-17.91, 10.69) %; p=0.622)]. The study was underpowered to reach level of statistical

477   significance for differences observed. Linear regression analysis adjusting for age, gender,

478   hemoglobin at admission, daily energy intake from RUTF, LOS in study and growth velocity

479   (supplemental **table 1** for full results of the linear regression) indicated that treatment with

480   SMS-RUTF was associated with a statistically significant greater increase in hemoglobin of

481    $0.670(0.420\text{-}0.921)$g dl^{-1} when compared to children treated using P-RUTF (p<0.001). The

482   difference of $0.743(0.427–1.059)$ g dl^{-1} when only children discharged as recovered were

483   included in the analysis was also significant (p<0.001).

484   ### *Amino acids*

485   At admission the overnight-fasting plasma concentrations of the tested free amino acids did

486   not differ according to the RUTF group. Comparison with community controls children

487   without acute malnutrition showed that malnourished children enrolled in both groups had

488   significantly reduced concentration of several of these AAs (**table 4).** Nutrition rehabilitation

489   with both SMS-RUTF and P-RUTF resulted in the replenishment of all the AAs tested by the

490   time of discharge, except for methionine (table 4). Stratified analyses showed that at the time

491   of discharge, in children aged 6-23 months the deficit was corrected for all the tested AAs,

492   whereas in older children, plasma concentration of both methionine and phenylalanine

493   remained lower than the community controls at the time of discharge (Supplemental **tables 2**

494   **and 3**).

495   ### *Body composition*

496   For children discharged as recovered, there were no differences at discharge between RUTF

497   groups or between the RUTF groups and the community controls in fat mass or fat mass index

498   in the DDT sub-study (**table 5**). By contrast, two by two comparisons of FFM indicated that

499   children after treatment with either of the two RUTFs had significantly lower levels of FFM

500   than the community controls (Table 5), but this difference disappeared after adjusting for

501   height.

502   The comparison of the BIA parameters between the sub-samples of SAM children tested at

503   admission and re-tested at the time of reaching MUAC 125mm, showed no significant

504   differences between children in the two intervention groups **(Supplemental table 4)**.

505   However, at discharge from the study, children in the SMS-RUTF group had higher IM and

506   lower FFMI, PhA and Xc/H compared to children in the P-RUTF group **(table 6)**. The SMS-

507   RUTF BIA subgroup also tended to have greater height than the P-RUTF BIA subgroup.

508   Technical challenges (lack of cooperation of children at the beginning of the nutrition

509   rehabilitation or presence of edema) limited the number of children with successful BIA

510   measurement at admission (43 surveyed out of the 200 selected) and at the time of reaching

511   12.5 cm of MUAC (57 children surveyed out of 200 selected) reducing the statistical power of

512   the BIA analysis at these time points. At discharge, the number of children surveyed was 164

513   children out of the 200 selected).

514   ***Linear growth***

515   Overall in this study there was no clinically relevant catch-up in height for age during

516   treatment and no significant differences in linear growth between the RUTF groups. The

517   severity of stunting in children aged 6 - 23 months at enrolment increased very slightly over

518   the study period, whilst in children aged between 24 - 59 months there was a small but

519   clinically insignificant improvement. Within group analysis showed that the daily increments

520   length gain were not different between children discharged as recovered and children

521   discharged as not-recovered **(Supplemental table 5)**.

522   **RUTF intake, acceptability and tolerance**

523   *RUTF intake*

524   The intake of RUTF was higher for children in the P-RUTF group. For children aged 6 - 24

525   months the mean(SD) daily intake was 183.2 (76.3) g/day for SMS-RUTF versus 207.8 (76.4)

526   g/day for P-RUTF, a difference(95%CI) of = -24.6 (-39.6, -9.6) g/day; p=0.001. For children

527   aged 24 – 59 months the mean(SD) daily intake was 243.8 (86.8) g/day for SMS-RUTF

528   versus 272.7 (77.9) g/day for P-RUTF, a difference(95%CI) of = -28.9(-43.94,-13.9) g/day;

529   p<0.001 **(Supplemental table 6)**

530   Energy intake was significantly higher in children aged 24-59 month receiving P-RUTF

531   compared to the same age group receiving SMS-RUTF [142.7 (50.8) kcal/kg/day for SMS-

532   RUTF group versus 157.2 (51.9) kcal/kg/day in the P-RUTF group, a difference of -18.63 (-

533   27.65, -9.51); p<0.001. The differences in energy intakes in the younger age group [149.5

534   (82.9) kcal/kg/day for SMS-RUTF group versus 165.7 (58. 7) kcal/kg/day for P-RUTF a

535   difference of -16.2(-30. 4, -2.0) kcal/kg/day was also significant; p=0.026. Within each

536   RUTF group and each age categories, the daily energy intake did not differ between those

537   who recovered and the non-respondent discharged as non-recovered (data not shown).

538   *RUTF acceptability*

539   The data on RUTF acceptability suggested that the only difference between the two RUTF

540   products was that fewer children below 24 months experienced flatulence on the SMS-RUTF

541   (supplementary table 6). Among those who defaulted, a dislike of the RUTF was reported in

542   19.2% (14/73) of the SMS-RUTF group versus 13.3% (6.45) in the P-RUTF group; p=0.411.

543   Among the same group side effects related to RUTF intake were 2.74% (2/73) in the SMS-

544   RUTF group versus 2.22% (2/45) in the P-RUTF group; p=0.862.

545

Discussion

547   Children with SAM need safe, palatable foods with energy, protein, fat, minerals and vitamins

548   tailored to their needs for restoration of normal body functions and catch up growth(32).

549   Providing P-RUTF tailored to body weight has been shown to successfully support catch-up

550   growth(2;44), but, P-RUTF is expensive and the high cost affects the coverage and the

551   sustainability of CMAM programs. Almost half of the cost of the P-RUTF is due to milk

552   powder that constitutes 25% to 30% of the content of P-RUTF and removing the milk from

553   RUTF has the potential to substantially reduce the cost of such products. Although predicting

554   saving accurately without undertaking actual commercial scale trials is difficult, our analysis

555   in Malawi, where the study foods were produced, suggests a 15% saving on finished product

556   cost. However, the saving is likely to vary from one year to another according to milk price in

557   local and global market and to the country of production.

558

559   This study has yielded important information regarding the efficacy of the no milk SMS-

560   RUTF. It has confirmed that SMS-RUTF is not inferior to P-RUTF in children ≥24 months of

561   age with respect to recovery rate, weight gain and length of stay and therefore can be used as

562   an alternative to P-RUTF.   Importantly the study has showed that treatment with both SMS

563   and P-RUTFs corrected amino acid deficiencies to a similar extent and both RUTFs were not

564   associated with excess of fat deposition. The BIA sub-study, confirmed substantial increases

565   in the FFMI in both groups bringing them back to a par with the community controls. In the

566   SMS-RUTF group the increase in FFMI was slightly less than in the P-RUTF corresponding

567   to the greater increases in length seen in this group. This minor difference in FFMI was

568   associated by a small difference that is unlikely to have any clinical importance in the markers

569   of FFM quality (phase angle, IM) that were also lower in the SMS-RUTF group, the greater

570   increase in hemoglobin produced by SMS-RUTF compared to P-RUTF also shows that it is

571   possible to improve the efficacy of RUTF formulations in correcting anemia. At the same

572   time, the study has provided evidence that children aged <24 months don't respond as well to

573   SMS-RUTF and that P-RUTF should continue to be used for this age group until a cheaper

574   alternative is developed.

575   .

576   The need of animal source food, especially of cow milk products, in food for management of

577   acute malnutrition including moderate and severe acute malnutrition is still subject of an on-

578   going debate (45-49). Several properties of milk including the high quality of the proteins, the

579   presence of bioactive factors, the minerals profile and the high lactose content are given as

580   reasons for the obligatory inclusion of a certain amount of milk in RUTF (49). As a result the

581   current UN guidelines specify that more than 50% of the protein in RUTF should be from an

582   animal source. However, several studies from industrialized countries have shown that in fast

583   growing infants, soya can successfully replace cow milk when there is medical or socio-

584   cultural contraindication to milk (50). Similarly, a study published in 1996 showed that the

585   effectiveness of soya milk and cow milk were similar in nutrition rehabilitation of SAM (51)

586   and we have previously demonstrated that it is possible to achieve the recommended nutrient

587   profile for RUTF without the inclusion of milk (52). The present study confirms our earlier

588   findings from Zambia that an SMS-RUTF containing no animal source protein is as effective

589   as P-RUTF in treating SAM in children 24 months or older(11). This finding has important

590   practical implications, indicating that the cost of the CMAM programs can safely be reduced

591   by using SMS-RUTF in all children above the age of two and restricting the more expensive

592   P-RUTF for use in children less than 2 years of age.

593

594   The reasons for the inferior response to the milk-free RUTF in children less than 2 years are

595   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

621   grow at more than10 g/kg/day (56). The increased plasma levels of free amino acids between

622   admission and discharge and compared to those seen in community controls indicates that the

623   two RUTFs supplied sufficient quantity of these amino acids. However, we did not measure

624   all the amino acids and the sample size did not allow testing a sufficient number of non-

625   recovered children. Thus, future research should still assess possible contribution of some key

626   amino acids in the poor physical growth in children below 24 months recovering from SAM.

627   A decreased bio-availability of essential nutrients is another possible cause for the inferior

628   response to the milk-free RUTF in the younger children. Phytic acid is a common plant

629   storage compound that binds divalent metallic ions preventing their absorption in the small

630   intestine that is not present in animal source foods. It is therefore theoretically possible that

631   the switch from milk to the grains and legumes could have increased the phytic acid content

632   of the SMS-RUTF decreasing the bio-availability of iron and zinc. We believe that this is

633   explanation is however unlikely. A recent laboratory analysis of different P-RUTFs found

634   huge variations in the phytic acid levels, that ranged from 1015mg/100g for P-RUTF

635   produced in Europe down to 371 mg/100g for P-RUTF manufactured in African countries

636   (57). The iron content of 10-14 mg/100g in the P-RUTF combined with these amounts of

637   phytic acid give phytic acid/iron ratios between 7– 13, far higher than the recommended

638   upper limit ratio of <1(58). By contrast, the production of SMS-RUTF included specific

639   measures to reduce phytic acid and to increase the content of iron. This resulted in a phytic

640   acid acid/iron ratio of 0.8. Based on evidence that increasing vitamin C improves absorption

641   of iron (59;60), the vitamin C content of the SMS was also increased to enhance the iron

642   bioavailability. The greater increase in hemoglobin amongst children receiving SMS-RUTF

643   suggests that these measures were effective in increasing iron absorption. The SMS-RUTF

644   also included more zinc compared to P-RUTF in order to bring the phytic acid/zinc ratios

645   towards international recommendations (see table 1). Specific iron and zinc absorption

646   studies should be done to confirm that the strategy used to improve bioavailability of these

647   minerals was sufficient.

648

649   Several studies have reported that tolerance of lactose declines naturally with age with the

650   prevalence of lactose intolerance increases sharply after the cessation breastfeeding at round

651   24 months of age (61;62). Indeed, post weaning genetically programmed and irreversible

652   reduction of lactase activity has been described worldwide (63). Thus increasing lactose

653   intolerance in the older children could explain the differences seen with the benefit of the

654   growth promoting nutrients present in milk increasingly counterbalanced by the negative

655   effect of lactose intolerance in the older children. However, as the response to treatment in

656   both the study arms was superior amongst children ≥24 months this explanation is unlikely. ,

657   a conclusion supported by the fact that several studies have previously reported similar

658   growth pattern in lactose intolerant children given lactose free dairy products compared to

659   lactose intolerant children given dairy products containing lactose (61;62).

660

661   Differences in the pathophysiology of SAM between the two age groups is likely to be

662   important in both the inferior response in the treatment of SAM and also the different the

663   linear growth response of the younger and older children that we observed. In this study, the

664   length for age in children below 24 months of age continued to decline during nutrition

665   treatment whereas in the older children some linear growth catch up was observed during

666   treatment. This suggest that the nutrient requirement for rehabilitation may not be the same

667   for children off different ages and it is likely that similar physiological differences are also

668   important reasons behind the inferior response to the milk-free RUTF in the younger children.

669   These findings highlight the need to enhance our understanding of the differences between

670   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

721 In this study the fat mass and the FFMI of children who recovered was comparable to that of

722 the community controls, suggesting that the differences in the absolute amounts of FFM could

723 be explained by differences in height. It is therefore possible the residual increased risk of

724 mortality post discharge after the treatment of SAM may be related to the degree of

725 stunting(86). The close inter-connections between acute and chronic malnutrition combined

726 with the relatively limited impact of short duration treatment with RUTF on stunting supports

727 the need to investigate integrated approaches towards acute and chronic malnutrition (87-89).

728 Such approaches that combine intensive initial nutrition rehabilitation to correct

729 weight/muscle deficit and prolonged nutrition support to re-establish FFM and sustain

730 recovery of linear deficit should be developed and their effectiveness in preventing relapse

731 and promoting linear growth and FFM catch ups assessed.

732

733 BIA analysis gave similar results to DDT regarding change in body fat, Fat Free mass and Fat

734 Free mass index. In addition the BIA analysis identified significant differences in cellular

735 membranes function indicators such as phase angle and wellness marker between children

736 treated with SMS-RUTF and those treated with P-RUTF. The clinical significance of the

737 observed differences is unknown and need further investigations but many studies have

738 demonstrated that Phase angle is an independent predictor of diseases and death in both

739 children and adults (90-94).

740

741 This study was conducted in a setting where all the ingredients are already commonly used in

742 the preparation of porridge for complementary feeding. Despite that, our findings can be

743 generalized as soya and maize have been used in food distributed during humanitarian crises

744 worldwide and existing evidence shows that the standard RUTFs is effective in children 6 to

745 59 months of age suffering from SAM of all continents even where peanut paste is not

746 commonly used in feeding infant and young children. Also, we enrolled children using

747 criteria universally used for enrollment in CMAM programs. However, our findings should

748 be interpreting taking into account some limitations. The main limitation is that we were

749 unable to measure the total daily nutritional intake and measured instead only RUTF intake.

750 Measuring total daily intake would have allowed us to better distinguish the effect of product

751 composition on satiety on the response observed in both under twos and over twos. Although

752 we doubt that the intake from home food or breast milk influenced the recovery, we were

753 unable to exclude it definitively. The second limitation is that we were unable to include

754 sufficient number of children who did not recover into the sub-studies evaluating the

755 evolution of amino acid profile or assessing body composition to allows determine if

756 differences in food quality such us in amino acid profile contributed to the differences

757 observed.

758

759 In conclusion, the present study has demonstrated that SMS-RUTF can be used to treat SAM

760 in children ≥24 months of age and that the iron content in RUTF should be increased. The

761 lower cost of manufacture of SMS-RUTF and its reliance on locally grown ingredients would

762 reduce the costs of CMAM programs and facilitate the production of RUTF in countries with

763 a high burden of SAM, especially because we have placed this recipe in the public domain

764 and put in place mechanisms preventing any entity from blocking access to it. The additional

765 iron would increase the efficacy of the product in the treatment of anemia associated with

766 SAM.

767 The study has also shown that there is a need for two products with different composition to

768 treat SAM. One for children under 2 years that ideally should also be optimized to promote a

769 reversal of stunting and one for the older children that should be formulated to maintain

770 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

784   **Conflict of interest:**

785   Valid Nutrition designed and produced the SMS-RUTF. PA is an employee of Valid

786   Nutrition. SC is the unpaid director of Valid Nutrition. Valid International is the sister

787   company of Valid Nutrition and BP and KS are Valid International employee. All the others

788   authors have no conflict of interest. The PRANA foundation and Irish Aid had no say on the

789   design, implementation and interpretation of the results. Valid Nutrition administered the

790   study grant. Valid Nutrition and Valid international researchers participated in study design

791   and implementation and in the interpretation of results.

792

Contribution of authors:

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

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

Amino Acid	Control[1] (A) Median(IQR[5])	SMS-RUTF[2](B) Median(IQR)	P-RUTF[3](C) Median(IQR)	Comparisons (p-values)[4]		
				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

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/m²)	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/m²)	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).

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

Enrollment

Assessed for eligibility (n= 924)

Excluded (n= 38)
- Not meeting inclusion criteria (n=2)
- Declined to participate (n= 12)
- Group assignment not random (n=6)
- Admission by unqualified staff (n=19)

Randomized to RUTF groups (n=886)
(0-23 month=414 /≥24 months=472)

Allocation

SMS-RUTF
Allocated to intervention = 445 (212/233)
- Received allocated RUTF=439(208/231)
- Post first day refusal = 6 (4/2)

P-RUTF
Allocated to intervention =441 (202/239)
- Received allocated RUTF=436(199/237)
- Post first day refusal = 5 (3/2)

Follow-Up

Per protocol discharge =353 (143/210)

Self-discontinuation =69 (51/18)

Programme termination =17 (14/3)

Per protocol discharge =378 (161/217)

Self-discontinuation =49 (31/18)

Programme termination =9 (7/2)

Analysis

Analysed

ITT analyses =439(208/231)

PP analysis: recovery rate: n=353 (143/210)
- Exclude self-discontinued n=69(51/18)

PP analysis: weight gain and LOS=317(113/204)
- Include only those discharged as cured
- Exclude deaths [n=11(7/4)] and Non-respondents [n=25(23/2)]

Analysed

ITT analyses = 436(199/237)

PP analysis: recovery rate=378 (161/217)
- Exclude self-discontinued [n=49(31/18)] and because still on treatment at programme end [n=9(7/2)]

PP analysis: weight gain and LOS=362(148/214)
- Include only those discharged as cured
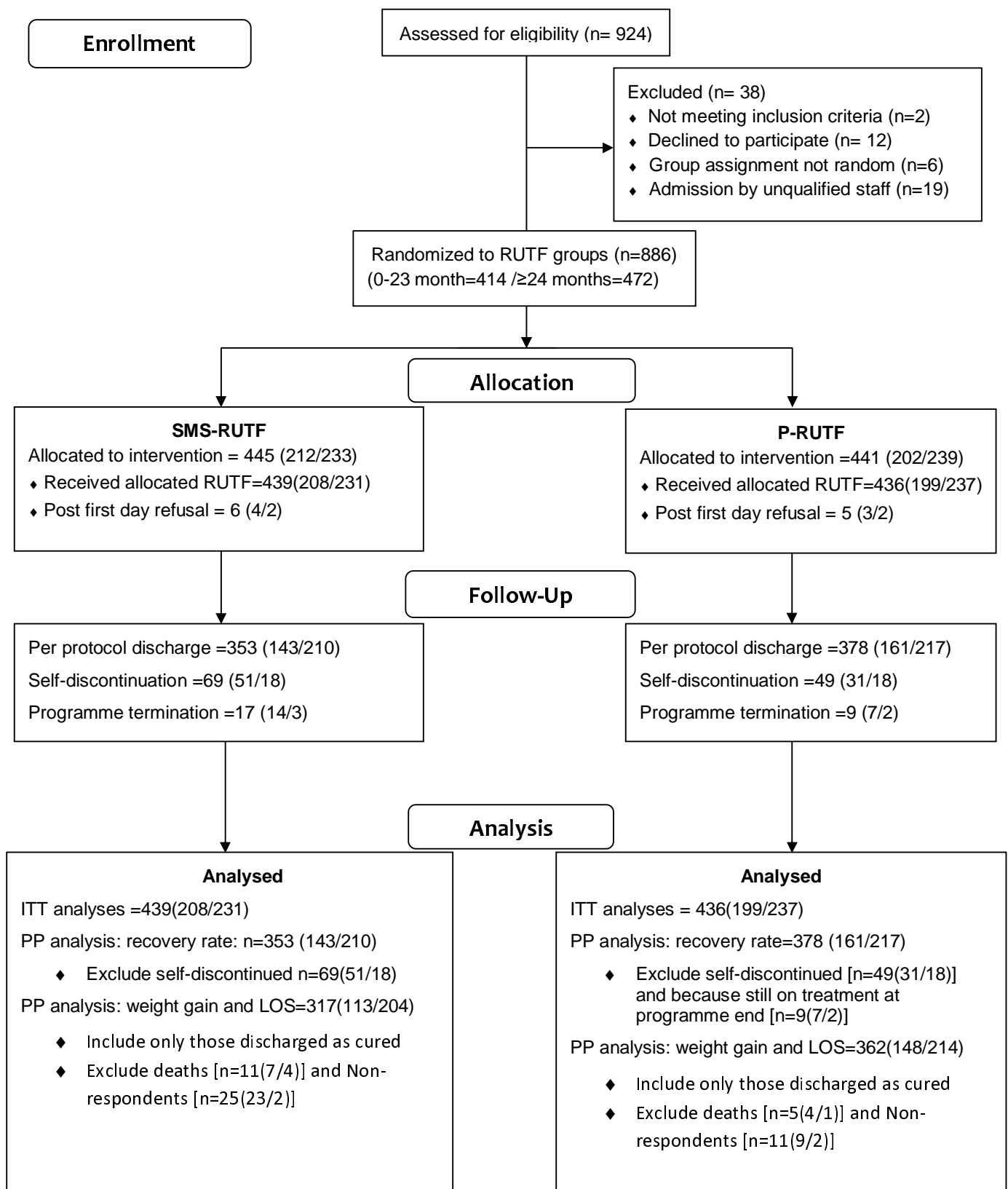- Exclude deaths [n=5(4/1)] and Non-respondents [n=11(9/2)]

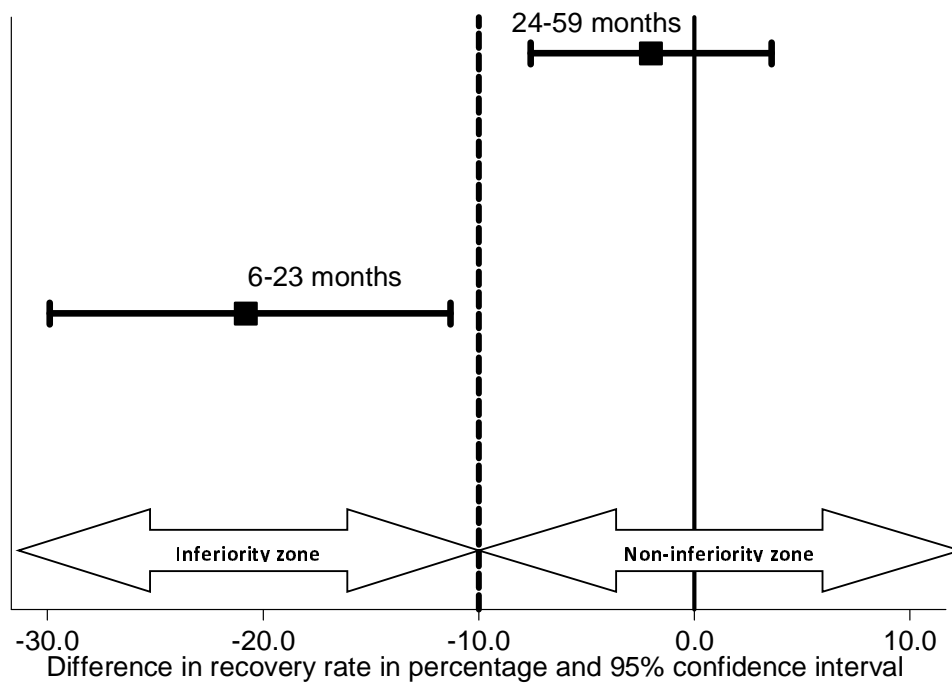Figure 1: study participants flow diagram

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
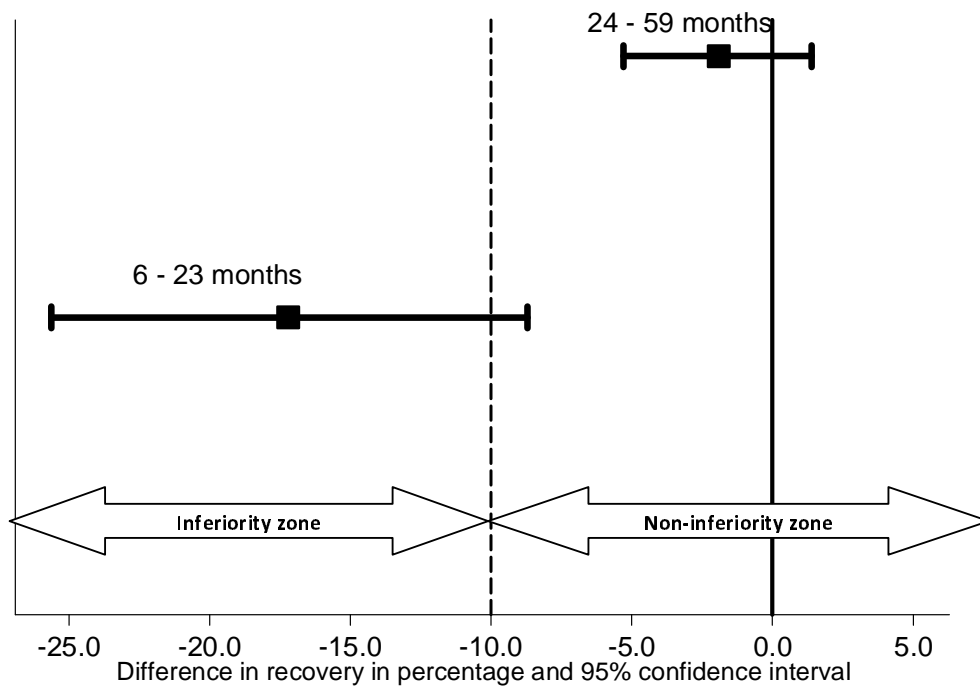
Figure 3: Per Protocol analysis: difference in recovery rate between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food [n=353(143/210)] and Peanut based Ready-to-Use Therapeutic Food [n=378(161/217)] for both age groups
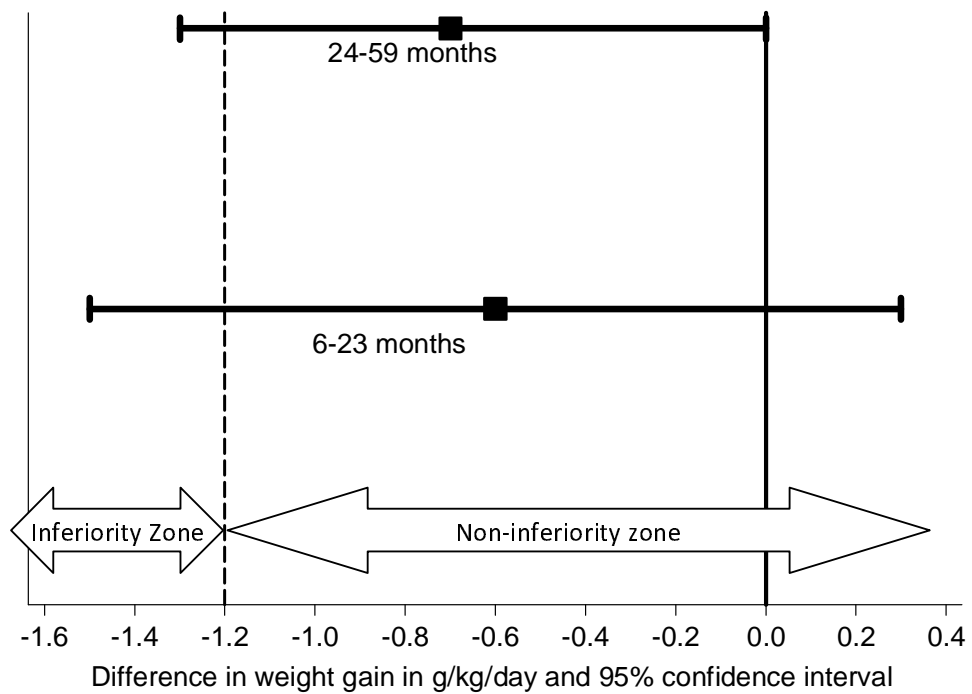
Figure 4: Per protocol analysis: difference in daily weight gain between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food [n=317(113/204)] and Peanut based Ready-to-Use Therapeutic Food [n=362(148/214)] for both age groups
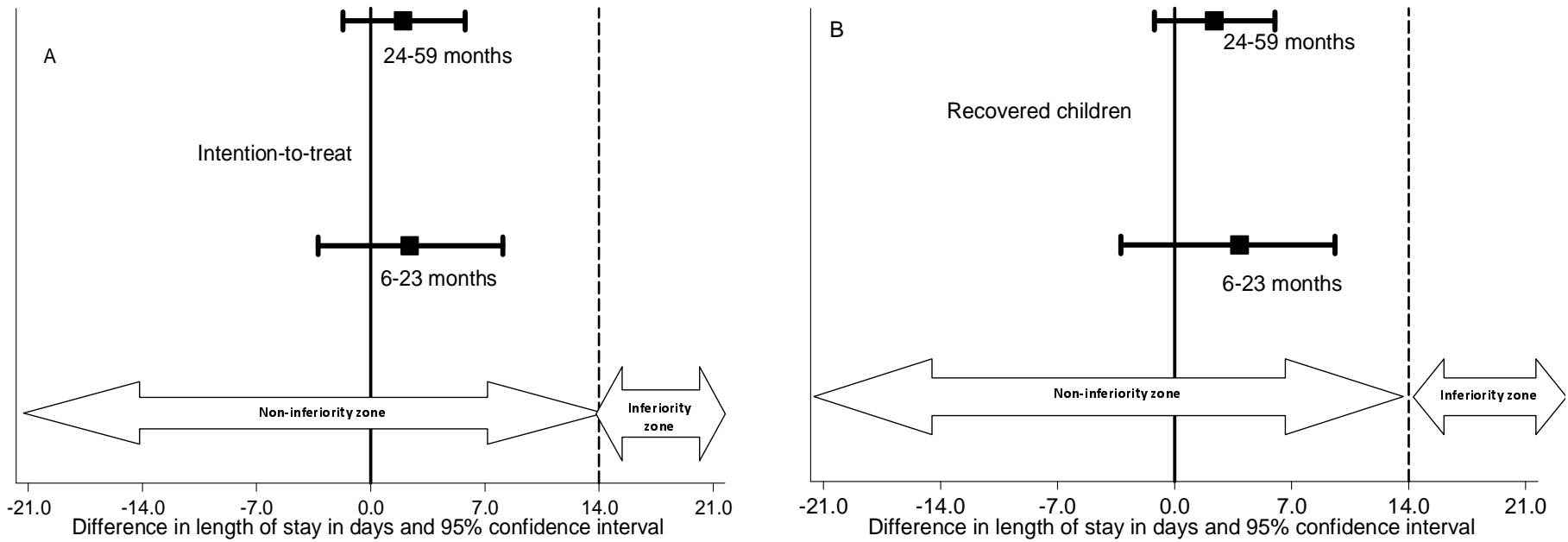
Figure 5: difference in length of stay between the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food [n=439(208/231)] and Peanut based Ready-to-Use Therapeutic Food [n=436(199/237)] for both age groups in intention-to-treat analysis (A) and difference between recovered children (B) of the Soya-Maize-Sorghum Ready-to-Use Therapeutic Food group [n=317(113/204)] and Peanut based Ready-to-Use Therapeutic Food [n=362(148/214)]