

## Applied nutritional investigation

## Development of a cross-over randomized trial method to determine the acceptability and safety of novel ready-to-use therapeutic foods

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## ARTICLE INFO

## Article history:

Received 21 December 2011

Accepted 2 April 2012

## Keywords:

Ready to use therapeutic food

Acceptability

Randomized trial

Preference

Safety

Crossover

## ABSTRACT

**Objective:** To develop a method for determining the acceptability and safety of ready-to-use therapeutic foods (RUTF) before clinical trialing. Acceptability was defined using a combination of three consumption, nine safety, and six preference criteria. These were used to compare a soy/maize/sorghum RUTF (SMS-RUTFh), designed for the rehabilitation of human immunodeficiency virus/tuberculosis (HIV/TB) wasted adults, with a peanut-butter/milk-powder paste (P-RUTF; brand: Plumpy'nut) designed for pediatric treatment.

**Methods:** A cross-over, randomized, controlled trial was conducted in Kenya. Ten days of repeated measures of product intake by 41 HIV/TB patients, >18 y old, body mass index (BMI) 18–24 kg·m<sup>-2</sup>, 250 g were offered daily under direct observation as a replacement lunch meal. Consumption, comorbidity, and preferences were recorded.

**Results:** The study arms had similar age, sex, marital status, initial BMI, and middle upper-arm circumference. No carryover effect or serious adverse events were found. SMS-RUTFh energy intake was not statistically different from the control, when adjusted for BMI on day 1, and the presence of throat sores. General preference, taste, and sweetness scores were higher for SMS-RUTFh compared to the control ( $P < 0.05$ ). Most consumption, safety, and preference criteria for SMS-RUTFh were satisfied except for the average number of days of nausea (0.16 versus 0.09 d) and vomiting (0.04 versus 0.02 d), which occurred with a higher frequency ( $P < 0.05$ ).

**Conclusion:** SMS-RUTFh appears to be acceptable and can be safely clinically trialed, if close monitoring of vomiting and nausea is included. The method reported here is a useful and feasible approach for testing the acceptability of ready-to-use foods in low income countries.

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## Introduction

Ready-to-use therapeutic foods (RUTF) are high-energy, nutrient-dense products in which the powdered ingredients are usually suspended in fat. They do not require any preparation or the addition of water before ingestion [1] and can be stored for long periods without refrigeration. They can be individually packaged and can therefore be used effectively in situations with non-optimal hygiene conditions [1]. RUTFs are popular in feeding programs [2], including human immunodeficiency

virus/tuberculosis (HIV/TB) interventions [1,3], because their use has been associated with an increase in successful treatment rates for severe acute malnutrition (SAM) when compared to other conventional treatments [4]. However, at present, the high price of RUTFs and their low regional availability hampers widespread use [5].

RUTF were initially developed for pediatric nutritional rehabilitation and the United Nations currently recommends [2,6] their use, at the community level, to help eradicate the one million child deaths that occur every year due to SAM [6]. In the next few years, \$US2.6 billion will be spent on SAM treatment [4,7], and therefore, novel, cheaper, culturally acceptable, efficacious, and regionally manufactured products are already in

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demand for this patient group [2]. RUTF have also been used in feeding programs for HIV and TB patients and evidence from low-resource settings [8–14] shows that HIV/TB wasting in adults is still a public health issue in Sub-Saharan Africa, despite the increasing access to antiretroviral therapy.

In such countries, HIV programs aiming for nutritional rehabilitation and/or nutrition support tend to use a few specific types of food [10], usually either fortified blended foods [15] or RUTFs [16]. The most common commercial brand of RUTF is Plumpy'nut [17], which was designed for pediatric use and is the only one that has been clinically tested in several different studies [3,18–22]. In wasted adults, a number of factors have been shown to reduce compliance with Plumpy'nut including the taste of this pediatric formulation [23]. Moreover, the micronutrient densities in Plumpy'nut might not be appropriate for the needs of wasted adults with HIV/TB. For these reasons, there is demand for the development of a novel RUTF for this patient group.

Changes to the formulation of RUTF should be based on clinical evidence derived from randomized controlled trials (RCT) [24] but these are costly to implement. Therefore, robust data on product acceptability are required before implementation of a RCT, and determining adequate consumption, safety, and preference is a crucial early step in successful product development. However, at present there is no internationally endorsed protocol to assess the acceptability of products of this kind.

Here, we present a method for testing the acceptability of novel RUTF. To our knowledge, this is the first trial in a developing country that tests the acceptability of this type of product in wasted adults. The results of this randomized control study are presented according to recommended guidelines for cross-over trials [25].

## Materials and methods

### Trial and control products

The control product (Plumpy'nut; Nutriset, Malaunay, France [17]) contains peanut butter, milk powder, and a premix of vitamins and minerals and is referred to here as P-RUTF. The trial RUTF (Valid Nutrition, Derry Duff, Ireland, at Insta Ltd., Nairobi, Kenya) contained soybeans, maize, and sorghum, no micronutrients premix, and is referred to here as SMS-RUTFh ("h" standing for adult HIV/TB). Both products contained sugar (28 and 15 100 g<sup>-1</sup>, respectively, for P-RUTF and SMS-RUTFh) and their macronutrients (energy, protein, lipids) closely met the United Nations requirements for RUTF (Table 1). Both their consistencies were pastelike, but their tastes and colors were different. The

detailed formulation and clinical efficacy of SMS-RUTFh will be reported in another article (in preparation).

### Study population, recruitment, and setting

The study was carried out in two locations, 2 km from each other, in Homa Bay, Kenya. The participants, enrolled after written informed consent, were patients recruited from the District hospital, supported by the Ministry of Health (MoH) and Médecins Sans Frontières-France (MSF). The patients from the two study groups met each other only at enrollment (day 1), and/or incidentally in the routine medical hospital visits. The participants, HIV and/or TB infected, were considered eligible if receiving antiretroviral therapy and/or TB treatment; age  $\geq 18$  y; and BMI between 18 and 24 kg·m<sup>-2</sup> (Table 2). The exclusion criteria consisted of previous enrollment in a nutritional therapeutic program; oral problems that prevented adequate swallowing (typical AIDS oral thrush was not an exclusion criteria); and any specific food intolerance (e.g., peanut allergy). Patients missing more than 3 d were considered defaulters.

### Study design

The study design was a two-arm cross-over randomized control trial. At enrollment, the patients were given a number from 1 to 2, randomly generated using an Excel spreadsheet (RAND function), that corresponded to one of the trial groups. Each group received one of the two products during each phase (AB/BA sequence). Under direct observation, during 2 wk (10 working days), water ad libitum and 250 g of one of the two products were offered to the patients as a replacement of the midday meal, with the message "please, eat as much as you wish." An extra 50 g was available on request. A maximum of 2 h was allowed to consume the product, and no leftovers could be taken away. After 2 wk (phase 1), the study was interrupted for 7 d (washout period) and then resumed for two more weeks (phase 2).

The professional background of the research staff included nursing, nutrition, and counseling. No one worked for the MoH or MSF, and the staff worked in a different study group each day, interviewing randomly assigned patients (ratio of staff members and patients: 1:3). In-depth questionnaires and focus group guidelines were provided in both English and the local language (Dholuo), after being anonymously back-translated. The packaging concealed the product identification.

### Study procedure and outcomes

To consider RUTFh acceptable and safe, it had to fulfill the following criteria and subcriteria for consumption, safety, and preference (Tables 3–5).

#### Criterion 1: Consumption

The consumption criterion consisted of three subcriteria. The subcriteria "average consumption" was satisfied if average SMS-RUTFh intake was more than 75% (187.5 g) of the offered amount within 1 h (criterion 1.1; Table 3), whereas SMS-RUTFh "daily consumption" was met if its intake was higher than 75% of the offered food for more than 75% of the days on the trial (criterion 1.2). Finally, the "comparative energy intake" criterion (1.3) was satisfied if the average energy intake per kilogram of body weight was significantly higher than 75% of the energy intake from the P-RUTF.

**Table 1**  
Comparison of macronutrients in the two RUTFs

	SMS-RUTFh		P-RUTF	References
Ingredients:	Soy beans, maize, sorghum, sugar, and oil		Peanut butter, milk powder, sugar and oil, vitamin and mineral premix	n.a.
Source:	International food composition databases	Laboratory results	Diop et al.(2003)	UN reference for pediatric RUTF (2007)
Reference number	[36,37]		[19]	[6]
Energy, kJ·kg <sup>-1</sup>	20 900	22 350	22 810	21 740–22 990
Protein, g·kg <sup>-1</sup>	120	153	136	n.a.
Protein/energy ratio, %	10	11	n.a.	10–12
Lipid, g·kg <sup>-1</sup>	310	336	357	n.a.
Lipid/Energy ratio, %	56	56	n.a.	45–60
( $\omega$ -6) Fatty acids/energy ratio, %	9	n.a.	n.a.	3–10
( $\omega$ -3) Fatty acids/energy ratio, %	0.8	n.a.	n.a.	0.3–2.5
Protein digestibility-corrected amino-acid score, %	82	n.a.	n.a.	n.a.

**Table 2**

Characteristics of the participants at the start of the study (day 1), unless specified otherwise

	Group	
	1 (n = 20)	2 (n = 21)
Females, n (%)	17 (85.0)	15 (71.4)
Age, y	34 (29; 42)	30 (27; 35)
Marital status, n (%)		
Currently married	10 (50.0)	12 (57.1)
Never been married	1 (5.0)	3 (14.3)
Previously married and now widower	9 (45.0)	6 (28.6)
BMI at enrollment, kg·m <sup>-2</sup>	20.3 (18.9; 22.1)	19.9 (19.1; 21.8)
MUAC at enrollment, mm	260 (229; 274)	266 (248; 280)
Diet Diversity Score <sup>†</sup>	7.5 (6.9; 8.2)	7.3 (6.7; 7.9)
Participants who had tasted P-RUTF at least once before the trial, n (%)	20 (100)	21 (100)

\* Median and inter-quartile range (IQR).

<sup>†</sup> Medians and IQR of four measures over 2 wk, two consecutive days per week (phase 2 of the trial).

#### Criterion 2: Safety

SMS-RUTFh was considered acceptable from the safety point of view if participants did not report any of five morbidity events more frequently than in the control product (criteria 2.1–2.5; Table 4). This parameter was expressed as the mean number of days in which morbidity events occurred during product consumption (10 d or less). Before the acceptability trial, microbiologic testing of SMS-RUTFh was performed. The results were in conformity with the United Nations specifications for such products [6].

#### Criterion 3: Preference

A product was considered preferred if its score was higher than the alternative in the following aspects: general preference, color, taste, sweetness, and texture (criteria 3.1–3.5; Table 5). At the end of the trial, each participant was asked to select the most preferred product (criterion 3.6), and two focus groups were held to investigate participants' experiences and perceptions that other methods may not have captured.

#### Data collection

Quantitative data were collected daily and included body weight, height, and middle upper-arm circumference (MUAC), weight of RUTF intake (Salter scale M021, max 500 ± 5 g), 24-h recall of nine clinical events, and individual eating duration. Body weight, MUAC, and height were collected daily, weekly, and at baseline, respectively. Individual interviews of all participants used a five-point Likert scale (with lower scores representing greater liking of a RUTF) [26], held to evaluate the preference for each product. Focus groups (30 to 40 min long) used preselected lists of discussion themes and the facilitators followed a written manual. Discussions undertaken in the local language were digitally recorded and transcribed into English, and twice a week, a diet diversity score (DDS) questionnaire (0–12 items type [27]) recorded the foods consumed at home.

#### Management of adverse events

Patients reporting any of the five clinical events for more than three consecutive days would have been immediately referred to the local clinic and withdrawn from the study if the cause was considered to be related to RUTF intake.

**Table 3**

Product consumption in the two combined groups (n<sub>1</sub> = 20; n<sub>2</sub> = 21)

	RUTF consumption*			P Value <sup>†</sup>	P Value <sup>‡</sup>
	SMS-RUTFh (n = 381)	P-RUTF (n = 398)	Threshold		
	A	B			
Average consumption, g·d <sup>-1</sup> (95%CI)	232.5 (218.9; 246.1)	243.0 (230.9; 255.0)	187.5 <sup>§</sup>	<0.001	<0.001
Daily consumption, % (95%CI)	86.1 (78.8; 93.4)	87.7 (81.4; 94.0)	75.0	<0.001	<0.001
Comparative energy intake kJ intake·kg body wt <sup>-1</sup> ·d <sup>-1</sup> (95%CI)	94.9 (81.5; 108.3)	102.4 (96.0; 108.7)	76.8 (72.0; 81.4) <sup>¶</sup>	<0.001	<0.001

\* Least-square means and 95% confidence intervals.

<sup>†</sup> P value between SMS-RUTFh and threshold.

<sup>‡</sup> P value between P-RUTF and threshold.

<sup>§</sup> The threshold is 0.75 times the 250 g initially provided.

<sup>¶</sup> Percentage of days with consumption higher than 75% of the provided amount (250 g).

<sup>¶</sup> The thresholds are 0.75 times the P-RUTF figures.

#### Sample size

A pediatric acceptability cross-over trial on RUTF [28] involved a sample size of 31 children, during 2 d of RUTF feeding, to detect a significant difference with  $\alpha$  and  $\beta$  errors of 0.05 and 0.95. Its power calculation, based on of RUTF daily intake, considered 1 SD an acceptable difference to be detected. However, because previous research on RUTF acceptability was not available in adults, the nature of our study was exploratory. For this reason, when compared to the Indian pediatric study, the sample size (n = 50 including dropouts) and the number of feeding days (10 repeated measures/RUTF/individual) were both increased, but limited by the available budget.

#### Statistical methods

Student's *t* test and regression models were used to test for differences between continuous data. The Wilcoxon rank-sum (Mann-Whitney) test and sign test were used for non-normally distributed, unpaired, continuous data, whereas the Wilcoxon matched-pairs signed-rank test was used for non-normally distributed, paired continuous data, including the Likert scale five-item score. The double-sided Fisher exact test was used to compare categorical data, and odds ratios and confidence intervals were calculated. A linear regression model compared the energy intake of the two products after adjusting for potential confounders, including clinical events, socioeconomic data, and anthropometry at enrollment. Logistic regression models explored if the preference for a product could be influenced by group membership. Analysis of ordinal score for preference criteria was based on logistic (not ordinal) regression, after regrouping the data into two categories (scores 1 and score 2, 3, 4, or 5 of 5). This was because of the instability of the model, due to too few cases when cross-tabulating outcomes and predictors. When applicable, regression models benefitted from the robust standard error approach [29], so that the participant's series of repeated measurements were considered as individual clusters. Absence of a carryover effect was checked before treatment-effects analysis, following a method described elsewhere [30]. Statistical comparisons were two-tailed, and all testing was conducted at  $\alpha = 0.05$ , on per protocol data. EpiData version 3.1 software (Copenhagen, Denmark) was used for data entry and data analysis was undertaken using Stata IC v.10.

#### Ethical issues

This acceptability and safety trial was embedded into a larger research program that had ethical approval granted by the Kenyan Medical Research Institute and National Ethical Review Committee (SSC No. 1414) to test the clinical effectiveness of SMS-RUTFh.

## Results

### Characteristics of the participants

On June 30, 2008, the study staff enrolled 51 patients (Fig. 1) into a 5-wk trial. Two patients were excluded because they lived too far. Twenty-four and 25 participants were randomly allocated into groups 1 and 2, respectively. During the first phase of the trial, eight patients defaulted for more than 3 d and were excluded. Two of them stopped coming after the second day of the trial for unknown reasons and could not be traced. Six

**Table 4**  
Safety criteria using 24-h morbidity recall in combined groups ( $n_1 = 20$ ;  $n_2 = 21$ )

Criteria	Number of days* during which morbidity events occurred		P value
	SMS-RUTFh ( $n = 381$ )	P-RUTF ( $n = 398$ )	
	A	B	
C2.1: Nausea	0.16 (0.05; 0.47)	0.09 (0.05; 0.14)	0.04
C2.2: Vomiting	0.04 (0.01; 0.19)	0.02 (0.01; 0.04)	0.03
C2.3: Stomach pain	0.14 (0.05; 0.38)	0.16 (0.10; 0.25)	NS
C2.4: Flatulence	0.13 (0.05; 0.36)	0.16 (0.09; 0.26)	NS
C2.5: Diarrhea	0.36 (0.03; 0.70)	0.31 (0.13; 0.49)	NS

NS, non-significant

\* Least-square mean and 95% confidence interval.

patients dropped out because of reasons not associated with product intake (transfer, other commitments). Forty-one patients successfully completed the study.

At admission, gender, marital status, BMI, and MUAC (Table 2) in the two groups were statistically similar. The DDS did not highlight any statistical significant difference in terms of kinds of food intake at household level, between the two groups. No difference was detected between the 2 wk DDS, nor within the same week for the same patients (Table 6). No carryover regarding amount and daily energy intake was reported ( $P > 0.05$ ).

#### Measurement of acceptability

##### Measurement of consumption

Both average and daily consumption measurements were above the threshold ( $P < 0.001$ ; Table 3) for SMS-RUTFh, confirming that all the patients consumed more than 75% of SMS-RUTFh within an hour (criterion 1.1); that acceptable consumption occurred on more than 75% of the trial days (criterion 1.2); and that its energy intake was higher than 75% of the P-RUTF intake in the two groups combined ( $P < 0.001$ ) (criterion 1.3).

A linear regression model (robust standard error, 40-cluster analysis;  $R^2 = 0.11$ ;  $P = 0.01$ ;  $N = 779$ ) showed that the difference between the energy intakes of the two products (SMS-RUTFh and P-RUTF) was not statistically significant ( $P = 0.06$ ) when adjusted for confounders identified by a stepwise analysis (initial BMI, negatively correlated with energy intake,  $P = 0.002$ ; presence of throat sores, negatively correlated,  $P = 0.13$ ). Other potential confounders, which showed no or very small influence in the explored model and were not included, were age, and days of

**Table 5**  
Criteria for food preference (Likert score type\*; five items) in the two groups ( $n_1 = 20$ ;  $n_2 = 21$ ), expressed on the last days of phase 1 and 2 of the trial

Criteria	SMS-RUTFh ( $n = 39$ )	P-RUTF ( $n = 41$ )	P value
C3.1: General preference			
Median (IQR)	1 (1; 2)	2 (2; 3)	<0.001
Mean (95%CI)	1.4 (1.2; 1.5)	2.4 (2.1; 2.8)	
C3.2: Color			NS
Median (IQR)	2 (1; 3)	2 (1; 3)	
Mean (95%CI)	2.0 (1.6; 2.4)	2.1 (1.7; 2.4)	
C3.3: Taste			<0.001
Median (IQR)	1 (1; 2)	3 (2; 4)	
Mean (95%CI)	1.5 (1.3; 1.8)	2.7 (2.3; 3.1)	
C3.4: Sweetness			<0.001
Median (IQR)	1 (1; 2)	3 (2; 4)	
Mean (95%CI)	1.7 (1.3; 2.0)	2.3 (2.5; 3.3)	
C3.5: Texture			0.02
Median (IQR)	2 (1; 4)	2 (1; 2)	
Mean (95%CI)	2.3 (1.8; 2.7)	1.7 (1.4; 1.9)	

NS, non-significant

\* The scores range from 1 (very good) to 5 (very bad).

diarrhea, nausea, and flatulence. However, the statistical power of the available sample size was likely to be relatively small.

#### Evaluation of possible morbidity effects

Most types of morbidity did not differ according to product consumption (Table 4). Also, the average number of days with reported nausea and vomiting in participants consuming SMS-RUTFh was low (0.16 and 0.04 d of illness; 381 repeated daily measures). However, when applying robust standard error analysis, the data showed that these morbidities were significantly more frequent than when subjects were consuming P-RUTF (0.09 and 0.02; 398 repeated measures;  $P = 0.04$  and 0.03). Nausea or vomiting never occurred for more than three consecutive days.

#### Measurement of patient's preference

Results from the fortnight interviews indicated higher scores for general preference, taste, and sweetness for SMS-RUTFh (criterion 3.1, 3.3, and 3.4;  $P < 0.001$ ; Table 5), whereas no product was preferred in terms of color (criterion 3.2). SMS-RUTFh texture was less preferred than the control (criterion 3.5;  $P = 0.02$ ).

On the last day of the trial, the whole sample ( $n = 41$ ) failed to identify a final preference (criterion 3.6) for a specific product ( $P = 0.8$ ). SMS-RUTFh and P-RUTF were preferred, respectively, by 52% (95%CI: 36; 69) and 48% (32; 64) of the participants. However for most patients, the preferred product was the one allocated to them in the first phase of the trial. For participants starting phase 1 with product A, the odds to prefer product A were 5.4 times (95% CI, 1.4–20.4) higher than for participants starting product A in phase 2 ( $P = 0.02$ ).

The two focus groups organized on the last day supported the findings from the quantitative data and also suggested that “SMS-RUTFh texture needed to be refined,” whereas “P-RUTF tasted salty” and “provoked more cases of flatulence.” Moreover the patients were “not happy about changing the product from phase 1 to 2, once they had got accustomed to the first provided product” and felt that “the products were increasing weight” and physical “strength,” “reducing hunger feelings.” No morbidity event was mentioned during the focus groups.

## Discussion

The present study demonstrated that most prestated criteria for acceptability of a novel RUF were satisfied, confirmed the utility of the proposed method and, at the same time, illustrated lessons that will contribute to improving future trials of a similar kind.

#### The acceptability of SMS-RUTFh

The findings of this study suggest that, in this participant group, SMS-RUTFh intake was adequate, and it was preferred in some regard to the current standard product. The patients could consume most of the trial product provided throughout the study, exceeding the selected threshold for adequate energy intake based on the control RUTF. Despite the higher (8%) energy density of P-RUTF, the energy intakes of the two products were statistically similar when adjusted for possible confounders, but the study might be underpowered to highlight a difference. Among the identified confounders, it can be speculated that throat sores reduce the swallowing capacity of the patients. A qualitative study on the compliance of the use of P-RUTF achieved a similar conclusion [23]. In SAM patients, cases of swallowing difficulty need to be detected early by medical staff and

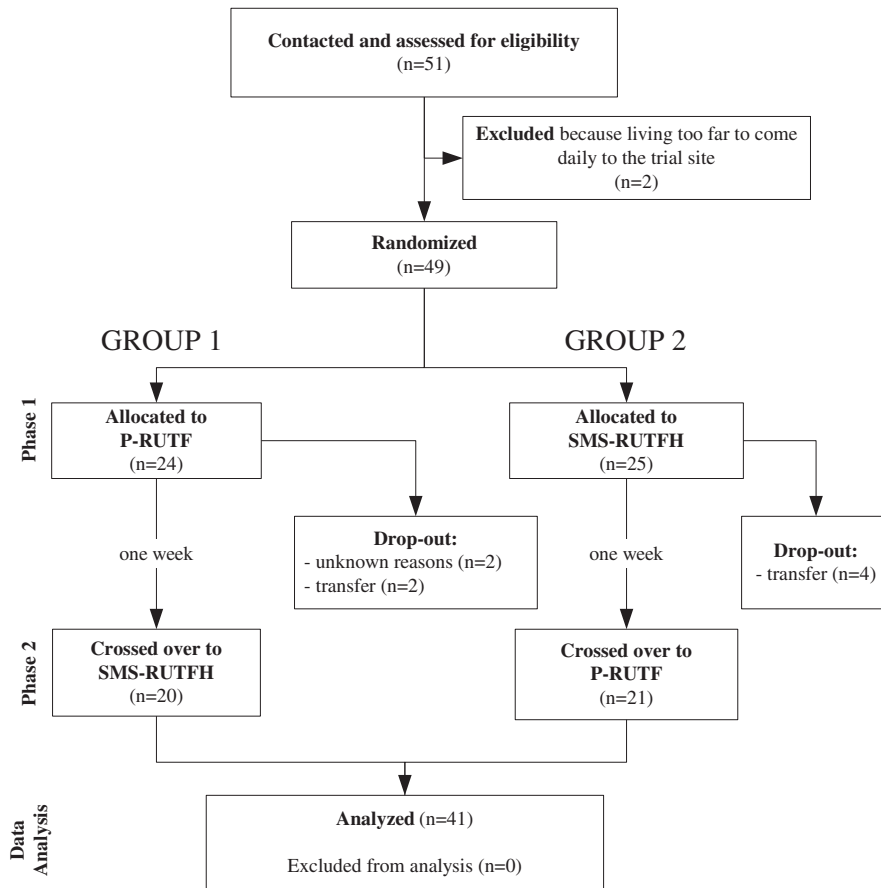


Fig. 1. Flow chart of the participants through the trial.

ideally addressed with appropriate in-patient care using therapeutic milk formulas (F75 and F100) [31]. As soon as the swallowing capacity is restored, generally in a few days, RUTF-based nutrition can be started and home-based care established.

The regression analysis found no evidence of increased morbidity associated with SMS-RUTFh consumption for most parameters. Although the frequencies of nausea and vomiting were higher in SMS-RUTFh than in the control product, they never affected participants for a prolonged period, and days of illness appeared to be scattered randomly along the time course of the trial. The regression models showed that the two comorbidities were not associated with a decreased energy intake. This suggests that the cause(s) might be due to chance or unknown factors, and that these and other events need close monitoring during the clinical trial.

The score for general preference was higher for SMS-RUTFh and its taste and sweetness were also preferred. However, its texture was less liked than P-RUTF, and this suggested the need

for improved industrial processing to enhance the SMS-RUTFh consistency.

The order the RUTFs were offered to the participants was important. SMS-RUTFh consumption increased or decreased, according to whether it was provided as the first or second product. That might be because it was difficult for participants to adapt to a novel product once they are accustomed to the previous one.

Some constraints were highlighted. The participants of the trial were enrolled in the MoH/MSF HIV program and had all been exposed to P-RUTF. Information of this kind, acquired before direct experience, could have shaped the food consumption and preferences as suggested elsewhere [32].

*Lesson learned about the method*

This study highlighted important aspects in the application of methods to assess RUF acceptability. Among these, the results confirmed that a combination of both quantitative and qualitative measures is needed to capture the complex of factors influencing acceptability. The carryover effect analysis, recommended in cross-over studies [25], showed that the washout period (1 wk) was adequate and might be reduced for future trials.

The sample size (n = 41) compares favorably with an Indian study, whose sample size was powered for a difference of at least 1 SD. Determining the equivalence or non-inferiority of SMS-RUTFh to the current standard product, rather than its statistical superiority to pre-stated thresholds, represents an alternative study design used to validate robustly a novel therapy [33] but requires a large

**Table 6**  
Diet diversity score\* in phase 2 of the trial

Week	1		2	
	Tuesday	Thursday	Tuesday	Thursday
Group 1 (n = 19)	7.4 (6.5; 8.2)	7.7 (6.9; 8.5)	7.4 (6.5; 8.3)	7.6 (7.0; 8.2)
Group 2 (n = 21)	7.8 (7.1; 8.5)	6.7 (5.9; 7.6)	7.7 (6.8; 8.6)	6.9 (6.7; 7.7)
Groups combined	7.6 (7.1; 8.1)	7.2 (6.6; 7.8)	7.6 (6.9; 8.2)	7.2 (6.7; 7.7)

\* Mean (95% confidence intervals).



sample size [34]. Other randomized trials [3,18,28], comparing RUTF with alternative food-based therapies, did not apply these methods. It is also important to note that the method described here is designed to be used in conducting an acceptability trial that precedes a RCT of clinical efficacy.

The study had some constraints. Ten days of RUTF intake, in each phase of our study, might have been too short to simulate the nutrition rehabilitation therapy in wasted adults (3 mo; MSF/Kenya, personal communication, 2008). The main use of RUTF is in outpatient and exclusive feeding programs. The study patients, instead, had access to the RUTF during only one daily meal, far from their households, while they were observed by the research staff.

For reasons explained elsewhere<sup>35</sup>, the SMS-RUTF did not contain the micronutrients premix, which might alter the final taste of the product and the findings of the trial. A taste comparison between RUTF with and without premix therefore must be carried out to confirm these acceptability results.

## Conclusion

Despite constraints, this exploratory study demonstrated the utility of this method and the acceptability of a novel, locally produced, RUTF. Its safety, mainly from the points of view of nausea and vomiting, should be monitored carefully. Lessons about the method were learned from the implementation of the study and should contribute to improving future trials.

## Acknowledgments

We thank P. Pomito, E. Severi, M. Wagah, N. Weldon, A. Wade, E. Koutoumanou, the study team, and the participants for their support of the study.

## References

- [1] Koethe JR, Chi BH, Megazzini KM, Heimburger DC, Stringer JS. Macronutrient supplementation for malnourished HIV-infected adults: a review of the evidence in resource-adequate and resource-constrained settings. *Clin Infect Dis* 2009;49:787–98.
- [2] Enserink M. Nutrition science. The peanut butter debate. *Science* 2008;322:555.
- [3] Ndekha MJ, van Oosterhout JG, Zijlstra EE, Manary M, Saloojee H, Manary MJ. Supplementary feeding with either ready-to-use fortified spread or corn-soy blend in wasted adults starting antiretroviral therapy in Malawi: randomised, investigator blinded, controlled trial. *BMJ* 2009;338:b1867.
- [4] Horton S, Shekar M, McDonald C, Mahal A, Brooks JK. Scaling-up nutrition. What will it cost? Washington, DC: The World Bank; 2010.
- [5] UNICEF, Valid International. Global CMAM mapping UNICEF supported countries. *Field Exchange* 2011;41:10–3.
- [6] WHO, WFP, UN/SCN, UNICEF. Community-Based Management of Severe Acute Malnutrition. Geneva: WHO; 2007.
- [7] United Nations. A road map for Scaling-Up Nutrition (SUN) 2010. Available at: <http://un-foodsecurity.org/node/768>. Accessed July 02, 2011.
- [8] Uthman OA. Prevalence and pattern of HIV-related malnutrition among women in sub-Saharan Africa: a meta-analysis of demographic health surveys. *BMC Public Health* 2008;8:226–30.
- [9] Koethe JR, Lukusa A, Giganti MJ, Chi BH, Nyirenda CK, Limbada MI, et al. Association between weight gain and clinical outcomes among malnourished adults initiating antiretroviral therapy in Lusaka, Zambia. *J Acquir Immune Defic Syndr* 2010;53:507–13.
- [10] Greenaway K. Food by Prescription: A Landscape Paper. Geneva: GAIN; 2009.
- [11] Paton NI, Sangeetha S, Earnest A, Bellamy R. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. *HIV Med* 2006;7:323–30.
- [12] Johannessen A, Naman E, Ngowi BJ, Sandvik L, Matee MI, Aglen HE, et al. Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. *BMC Infect Dis* 2008;8:52.
- [13] Stringer JS, Zulu I, Levy J, Stringer EM, Mwangi A, Chi BH, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *JAMA* 2006;296:782–93.
- [14] Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. *AIDS* 2006;20:2355–60.
- [15] WFP. Food and nutrition handbook. Rome: WFP; 2000.
- [16] Valid International, Concern Worldwide. Community-based Therapeutic Care (CTC): A Field Manual. Oxford: Valid International; 2006.
- [17] Nutriset. Plumpy'nut®. Available at: <http://www.nutriset.fr/en/product-range/produit-par-produit/plumpynut-ready-to-use-therapeutic-food-rutf.html>. Accessed July 02, 2010.
- [18] Diop el HI, 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;78:302–7.
- [19] Manary MJ, Ndekha MJ, Ashorn P, Maleta K, Briend A. Home based therapy for severe malnutrition with ready-to-use food. *Arch Dis Childhood* 2004;89:557–61.
- [20] Sandige H, Ndekha MJ, Briend A, Ashorn P, Manary MJ. Home-based treatment of malnourished Malawian children with locally produced or imported ready-to-use food. *J Pediatr Gastroenterol Nutr* 2004;39:141–6.
- [21] Bahwere P, Piwoz E, Joshua MC, Sadler K, Grobler-Tanner CH, Guerrero S, et al. 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.
- [22] Fergusson P, Tomkins A. HIV prevalence and mortality among children undergoing treatment for severe acute malnutrition in sub-Saharan Africa: a systematic review and meta-analysis. *Trans R Soc Trop Med Hyg* 2009;103:541–8.
- [23] Dibari F, Bahwere P, Le Gall I, Guerrero S, Mwaniki D, Seal A. A qualitative investigation of adherence to nutritional therapy in malnourished adult AIDS patients in Kenya. *Public Health Nutr* 2012;15:316–23.
- [24] Oakley E, Reinking J, Sandige H, Trehan I, Kennedy G, Maleta K, et al. A ready-to-use therapeutic food containing 10% milk is less effective than one with 25% milk in the treatment of severely malnourished children. *J Nutr* 2010;140:2248–52.
- [25] Mills EJ, Chan AW, Wu P, Vail A, Guyatt GH, Altman DG. Design, analysis, and presentation of crossover trials. *Trials* 2009;10:27.
- [26] Ling AM, Horwath C. Self-efficacy and consumption of fruit and vegetables: validation of a summated scale. *Am J Health Promot* 1999;13:290–8.
- [27] FANTA. Dietary Diversity as a Household Food Security Indicator. Washington DC: Fanta; 2002.
- [28] Dube B, Rongsen T, Mazumder S, Taneja S, Rafiqui F, Bhandari N, et al. Comparison of ready-to-use therapeutic food with cereal legume-based khichri among malnourished children. *Indian Pediatr* 2009;46:383–8.
- [29] Kirkwood B, Sterne J. Essential medical statistics. Oxford: Wiley-Blackwell; 2003.
- [30] Jones B, Kenward MG. Design and analysis of cross-over trials. London: Chapman and Hall; 2003.
- [31] WHO. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva: WHO; 1999.
- [32] Costell E, Tarrega A, Bayarri S. Food Acceptance: The Role of Consumer Perception and Attitudes. *Chemosensory Perception* 2010;3:42–50.
- [33] Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. *Lancet* 1999;354:13–9.
- [34] Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA* 2006;295:1152–60.
- [35] Dibari F, Diop EHI, 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.
- [36] University of California. World Food Dietary Assessment System. Version 2. Berkeley: University of California; 1998.
- [37] Nutrisurvey. Nutrition Surveys and Calculations. Guidelines, Software and additional Information 2007. Available at: <http://www.nutrisurvey.de>. Accessed October 10, 2007.