



Expert Meeting on Ready-to-Use-Therapeutic Foods (RUTF)  
UNICEF, Supply Division | Report 1 | 2<sup>nd</sup>-3<sup>rd</sup> September 2019



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## EXECUTIVE SUMMARY

A two-day technical meeting was held to enable discussion on what kind of information is needed for procurement agencies to assess new formulations of RUTF and to address concerns about Vitamin A levels in RUTF.

UNICEF coordinated the meeting with experts, from a diverse background including representation from WHO, FAO, WFP, MSF, USAID, Copenhagen University and a representative from the South African National Department of Health. The purpose of the meeting was to hear expert advice on the development of quality standards, product specifications and evidence requirements, specifically for alternative recipes of RUTF.

The discussion of this technical meeting centred on RUTF products that use cereals, seeds or legumes as alternatives to peanuts while complying with the nutritional composition including the specification on the minimal content of dairy proteins within the reference document *Community-Based Management of Severe Acute Malnutrition Joint Statement*<sup>1</sup>, from here known as “The Joint Statement”.

The meeting included discussions on the possible raw materials that could be used in RUTF alternative formulations and their relative content of antinutrients and the management of these factors in the finished product. Antinutrients such as phytic acid, protease and lipase inhibitors are reported to have implications in the nutritional value of food and therefore need to be controlled. It was proposed that a maximum limit would be included in future RUTF specifications to control the risk of antinutrients.

A working definition of a new RUTF product was developed in the meeting.

To enable products to be ready to be used in nutrition programs the group discussed criteria for assessment and the need for evidence of effectiveness of the formulation. A trial design for new formulations was outlined.

The current scientific literature on formulations of RUTF comprise of acceptability studies and effectiveness studies using randomized controlled trial designs. A two- by two cross-over acceptability trial design was proposed by the experts as the most suitable trial design to detect if there was any difference in the new versus the standard formulations. The main outcome of interest would be the RUTF consumption over the designated study period, by the target population and any adverse events.

The final topic discussed by the expert group was the challenges in maintaining vitamin A levels within the specified current limits (0.8-1.1 mg per 100 grams) in RUTF throughout the supply chain and shelf life period.

A comprehensive supply chain approach was suggested to address the decrease in vitamin A in RUTF. It was recommended to promote vitamin A testing i) during premix goods receipt, before using the premix in manufacturing RUTF and ii) post-production (batch release). Increasing the upper limit in the specifications of vitamin A in RUTF was

also discussed and the experts agreed that the maximum limit could be safely raised to 1.6 mg per 100 grams.

## MEETING PURPOSE

The purpose of the technical expert meeting held by UNICEF was to provide access to expert advice for UNICEF, procuring partners and governments for the development of quality standards, product specifications and evidence requirements, specifically for alternative recipes of RUTF. The meeting enabled UNICEF and partners to develop a road map for scientific evaluation and assessment of implementation of newer generation of RUTF formulations. The conclusions of this expert meeting will help to inform manufacturers of formulation requirements and provide clear guidance to manufacturers, governments and programs about what kind of trial design and scientific evidence is needed for alternative recipes.

## BACKGROUND

Since its initial use in emergencies, Ready to Use Therapeutic Foods (RUTF) have gained significant traction in programs enabling millions of children to be treated. UNICEF works with around 16 local producers who made this product in countries across Asia, Africa and the Americas. As of 2019, over 60 % of the RUTF supplies that UNICEF buys come from local manufacturers, close to beneficiaries.

In 2015, UNICEF's proposal for a RUTF Codex Guideline was accepted at the Codex Committee for Nutrition and Special Foods for Dietary Uses (CCNFSDU). During the discussion of the proposal, several member states emphasized the importance of a locally adapted guideline, that would include the incorporation of local ingredients to ensure products were suitable to the national customs, culture and to minimize inclusion of imported products.

In parallel to the work on the Codex Guideline for RUTF, the literature on RUTF started to feature alternative recipes of RUTF, with different combinations of cereals, grains or legumes being used in studies aiming to reduce cost, incorporate more local ingredients and provide more acceptable products to undertreated populations.

A 2-day Technical Expert Meeting was held to enable discussion of what kind of information is needed for procurement agencies to assess new formulations, the criteria for assessment and to discuss the kind of trial design new formulations require to enable products to be ready to be used in nutrition programs.

The discussion of this technical meeting centred on three different categories of new products:

**Renovation:** products that use a combination of alternative cereals, legumes or grains as partial or full replacement to peanuts in the standard formulation, in addition to 50% proteins sourced from dairy. These formulae are compliant to the 'Joint Statement'.

**Innovation:** this category uses a combination of cereals, legumes, grains and different sources of animal proteins – such as fish, egg or insect proteins. These formulae do not comply with the ‘Joint Statement’.

**Novel:** products that include a combination of cereals, legumes or grains in addition to added amino acids and/or possibly different levels of the vitamins and minerals. These formulae do not comply with the ‘Joint Statement’.

## UNICEF 2019 RUTF TENDER FOR ALTERNATIVE RECIPES

UNICEF tender for RUTF conducted over the end of 2018 and early 2019 included acceptable offers of alternative recipes of RUTF from 15 manufacturers, along with an outline on the variety of different ingredients in the new formulations. This is the first time UNICEF considered offers for alternative recipes for financial and technical evaluation.

### OVERVIEW OF UNICEF’S SPECIFICATION DEVELOPMENT PROCESS

The development of specifications is an important task as it provides the framework of product attributes that are then assessed in the technical evaluation of products. Typical attributes of products are included in specifications (Annex 1a). UNICEF procurement specifications are often shared amongst other agencies, and thus can have a wide influence, so several inputs are used to ensure that they adequately describe the product characteristics needed for the product’s use.

The review and development of new specifications also includes ensuring they are up to date with existing international references and that any new requirements are achievable by the supplier base (See Annex 1B).

### OVERVIEW OF UNICEF’S VALIDATION PROCESS

#### Technical Evaluation for Alternative RUTF Recipes

Performing technical evaluations and auditing manufacturers are the basis for the assessment of products and suppliers prior to procurement by UNICEF. The UNICEF quality assessment of nutrition products consists of 2 stages: dossier review and product sample evaluation and then followed by a facility GMP audit.

In addition to the evaluation process, UNICEF performs comprehensive testing once every year and Pre-Delivery Inspection (PDI) on all batches procured by UNICEF. To communicate the UNICEF requirements, a combination of webinars, pre-tender conferences, detailed specifications that include all reference standards are provided to enable suppliers to adhere to UNICEF standards.

#### Dossier Review

Dossiers from suppliers are reviewed for compliance against the specification. The Specialized Food Manufacturers Product Questionnaire is used as a guide for assessment.

## Product Sample Evaluation

Evaluation of nutritional product, the primary and secondary packaging materials, the product itself as well as the product label and an organoleptic taste test is conducted to assess the characteristics for acceptability. The organoleptic testing performed on nutrition products is a simple assessment aimed at ensuring the product meets the specification criteria for organoleptic properties (flavour, texture, odour and other sensorial characteristics).

## GMP Compliance

Following an acceptable technical evaluation of the product, if an inspection has not been conducted, then this is arranged. The quality audit follows Interagency Specialised Food Manufacturers Quality Questionnaire format and this questionnaire is shared with suppliers to prepare for the audit.

Quality audits use Codex references, specifically the *Code of Hygienic Practice for Low-Moisture Foods*, CXC 75-2015; (Amended, 2018) and *Recommended International Code of Practice - General Principles of Food Hygiene*, CAC/RCP 1-1969, (Rev. 3, 1997).

## **ORGANOLEPTIC PROPERTIES AND ANTINUTRIENTS IN RUTF ALTERNATIVE FORMULATIONS**

### **Organoleptic Evaluation of New Alternative RUTF Formulations.**

The organoleptic requirements stated on the UNICEF's specification for RUTF alternatives (Annex 2) were used as parameters for short listing samples of RUTF alternatives submitted in the tender.

The criteria included aspects of taste, homogeneity and granularity. Out of 19 samples included in the organoleptic testing, 11 were shortlisted. The results obtained from this pre-selection were presented to the technical expert group, along with the product samples. The questionnaire used by the participants can be found in Annex 3 for details.

## Antinutrients in RUTF

The review and discussion of the raw materials used in the different RUTF alternatives led to a debate on the topic of antinutrients, which are present in many of the raw materials used in the RUTF formulations. (see Popova and Dasha Mihaylova, 2019)

**Table 1. Antinutrients in different foods [29, 68 - 80].**

Source	Type	Amount
Legumes (soya, lentils, chick peas, peanuts, beans)	Phytic acid	386-714 mg/100g
	Saponins	106-170 mg/100g
	Cyanide	2-200 mg/100g
	Tannins	1.8-18 mg/g
	Trypsin inhibitor	6.7 mg/100g
	Oxalates	8 mg/kg
Grains (wheat, barley, rye, oat, millet, corn, spelt, kamut, sorgho)	Phytic acid	50-74 mg/g
	Oxalates	35-270 mg/100g
Pseudo-grains: quinoa, amaranth, wheat, buckwheat, teff	Phytic acid	
	Lectins	0.5-7.3 g/100g
	Saponins	0.04-2.14 ppm
	Goitrogens	
Nuts: almonds, hazelnut, cashew, pignola, pistachio, brazil nuts, walnuts, macadamia, etc.	Phytic acid	150-9400 mg/100g
	Lectins	37-144 µg/g
	Oxalates	40-490 mg/100g
Seeds: sesame, flaxseed, poppy seed, sunflower, pumpkin	Phytic acid	1-10.7 g/100g
	Alpha-amylase inhibitor	0.251 mg/mL
	Cyanide	140-370 ppm
Tubers: carrot, sweet potato, Jerusalem artichoke, manioc (or tapioca), yam	Oxalates	0.4-2.3 mg/100g
	Tannins	4.18-6.72 mg/100g
	Phytates	0.06-0.08 mg/100g
Nighshades: potato, tomato, eggplant, pepper	Phytic acid	0.82-4.48 mg/100g
	Tannins	0.19 mg/100g
	Saponins	0.16-0.25 mg/100g
	Cyanide	1.6-10.5 mg/100g

**Table 1:** Antinutrients in Plant-based Foods: A Review in *The Open Biotechnology Journal* · July 2019

Antinutrients are components that can bind to and capture micronutrients (mainly essential minerals) and amino acids or proteins contained in the RUTF formulations, making them unavailable for absorption in the digestive tract which results in a lower total nutritional value of the RUTF product<sup>ii</sup>. Some examples of antinutrients are phytic acid, protease and lipase inhibitors, saponins, cyanides, tannins, goitrogens, oxalates, trypsin inhibitors and lectins, among others.

Research has shown that the levels of antinutrients contained in a raw material can be significantly reduced by processing of the raw material using methods such as fermentation, roasting and extrusion. In a literature review on the effect of phytic acid as an antinutrient, it was found that some preparation methods such as milling, soaking, germinating, or fermenting can lower the content of phytic acid and protease inhibitors in foods. In the case of nuts and legumes, soaking and germinating may be more adequate, whereas for grains and cereals, all methods mentioned above are considered effective<sup>iii</sup>. Additionally, a different review has also shown that the presence of bioavailable

micronutrients can be increased by reducing phytic acid in foods through pre-treating the raw materials with methods such as milling, hulling, roasting, fermentation, soaking, germination. Moreover, by treating the raw materials with phytase enzymes<sup>iv,v</sup>. Particularly for chickpeas, nutritional properties are enhanced if they are previously pressure cooked or roasted, due to the reduction of the phytic acid content through these processes<sup>vi</sup>.

Since antinutrients are also present in peanut based RUTF formulations, as peanuts contain significant levels of phytic acid<sup>vii</sup> (Schlemmer et al., 2009), the level of antinutrients present in a standard (peanut based) formulation could be used as a reference upper limit value for all alternative formulations as this was agreed to be the most realistic level achievable.

## DISCUSSION ON BIOAVAILABILITY OF MICRONUTRIENTS IN SPECIALIZED NUTRITIOUS FOODS

In considering new recipes used in the management of severe acute malnutrition, one of the key issues to address is the relative bioavailability of nutrients in the alternative recipe matrix. The intestine lining and therefore absorptive capacity in children with wasting is not the same in normal and healthy children. Moreover, children with wasting are known to have lower gastric acidity, pancreatic insufficiency, and nutrient absorption.

Study findings on the values of bioavailability of minerals in human subjects (not with wasting) after consuming foods with micronutrient-fortified rice were shared with the group along with the laboratory testing methods for consideration.

For some micronutrients such as Iron and Zinc, the only possible measure for evaluating their absorption will be by specific absorption method such as radio labelling. Usually some micronutrients are not tested directly but other representative micronutrients are used as tracers. Methods such as radio labelling can be an expensive way to measure the bioavailability of a component. Newer methods using biomarkers have more recently been used to indicate intake and utilisation. The group also noted that bioavailability of nutrients is an important gap in our knowledge of effective micronutrient delivery and that none of RUTF formulations that are currently used in programs have gone through this kind of assessment, despite the importance of this research question.

For RUTF, if the product needs to be tested in the digestive system of SAM children, some non-invasive techniques (by assessing stools) could be considered for assessing absorption in SAM children, but obtaining the samples will be challenging. Measurement of weight gain as a proxy assessment for nutrient absorption in SAM children and assess micronutrient status at the end of a treatment (ideally before and after the treatment) was proposed as an alternative method. In summary, it is a complex task to measure micronutrient status in children after consumption of RUTF and this would be challenging to include in an acceptability trial for the new formulations. Given this complexity, the requirement to conduct bio-availability studies on new recipes of RUTF when the current peanut product has not had this level of assessment was considered unrealistic unless a convenient method was identified.

## DEFINITION AND PREREQUISITES FOR NEW RUTF PRODUCT

The development of a definition of what would constitute a new formulation that complies to the Joint Statement and what their pre-requisite criteria for these new products is summarised in the below bullet points:

1. Definition of a what constitutes a new product that complies with the Joint Statement:

- ✓ Any new addition of ingredient class<sup>1</sup>
- ✓ Any significant change (more than 10%) of class of bulk ingredient that is likely to alter the organoleptic properties from the previous product (this excludes changes in additives, vitamins and minerals premix, and other processing aids.)

## 2. Pre-requisites for new formulations:

New RUTF formulations should:

- i. Be compliant with WHO and Codex guidelines and standards
- ii. Meet interagency specification requirements **Error! Bookmark not defined.**
- iii. Be produced in a facility that meet interagency quality requirements<sup>2</sup>
- iv. Have antinutrient factors lower than the current peanut RUTF and cereal (BP100) versions
- v. Have shelf life claim supported by stability data
- vi. Have an acceptability study or efficacy study depending on the formulation and if feasible, bioavailability studies
- vii. Be monitored in the field to collect product related feedback.

The group agreed that the UNICEF process of evaluation in addition to the addition of anti-nutrient testing, would enable new formulations to be viewed as equal to the peanut product in terms of their nutritional profile once they passed through these steps of evaluation and anti-nutrient testing.

## SCIENTIFIC EVIDENCE ON NEW FORMULATIONS OF RUTF

### ACCEPTABILITY TRIALS

In preparation for the meeting, a literature review was conducted to present the evidence base on RUTF renovation (Annex 4). This included mostly peer-reviewed articles from 2010 with a focus on the renovation category. The studies represented 4 countries in Africa (Malawi, Ghana, Kenya, Ethiopia) and 5 in Asia (Vietnam, Bangladesh, Iran, India, Pakistan). The new RUTF varieties used a range of different ingredients such as sorghum, maize, soy, mung beans, lentils and oats replacing peanuts or reducing the amounts of peanuts in the RUTF. A recent study in Sierra Leone with a RUTF based on oats showed promising results and a potential price reduction. Many studies had used linear programming tool<sup>3</sup> to develop optimized country-specific, locally produced RUTF formulations e.g. in Ethiopia/Ghana/Pakistan/India<sup>viii</sup> and Sierra Leone<sup>xiii</sup>. Overall studies could be divided into two categories:

1. **Acceptability studies** with cross-over designs in children with MAM or children from food insecure populations. Studies compared new varieties of RUTF with standard

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<sup>1</sup> See annex 4

<sup>3</sup>Linear programming tool- Linear Programming (LP) can be used to solve questions on matching diets to nutritional and other additional constraints with a minimum amount of changes. Linear programming is a mathematical technique that allows the generation of optimal solutions that satisfy several constraints at once

<sup>2</sup> See Annex 1a and Annex 2.

RUTF through different measures of acceptability as the outcome of interest (amount of consumption, eagerness to eat, organoleptic properties etc.). The results were based on quantitative measures (weighing of sachets) and qualitative information (focus group discussions and interviews). The studies also looked at adverse effects such as diarrhea, vomiting, rash etc. Sample sizes were based on strength required to detect difference in outcomes of interest (generally 25 - 40 children).

2. **Effectiveness/efficacy-like trials** with randomized, controlled, double blinded set-ups including non-inferiority trials, equivalence trials etc. comparing standard RUTF with alternatives. Study populations were children 6-59 months with SAM enrolled in standard Community-Based Management of Acute Malnutrition (CMAM) programs. Sample sizes were based on the strength required to detect a difference in the outcome such as length of stay, weight gain and recovery (and other program outcomes) along with a secondary focus on adverse effects. Sample sizes varied between 1200/1300 children for recovery rates-focused studies and 260-300 children for studies looking at weight gain.

The expert group had an in-depth presentation and analysis of three acceptability studies from Ethiopia/Pakistan/India/Ghana<sup>viii</sup>, Malawi<sup>ix</sup> and Kenya<sup>x</sup> and four Randomized Controlled Trials from Malawi<sup>xi</sup>, Ghana<sup>xii</sup>, Sierra Leone<sup>xiii</sup> and Bangladesh<sup>xiv</sup>. Study design and methodological approach, study populations, outcomes of interest (recovery, weight gain on other aspects) and related sample sizes were compared and discussed.

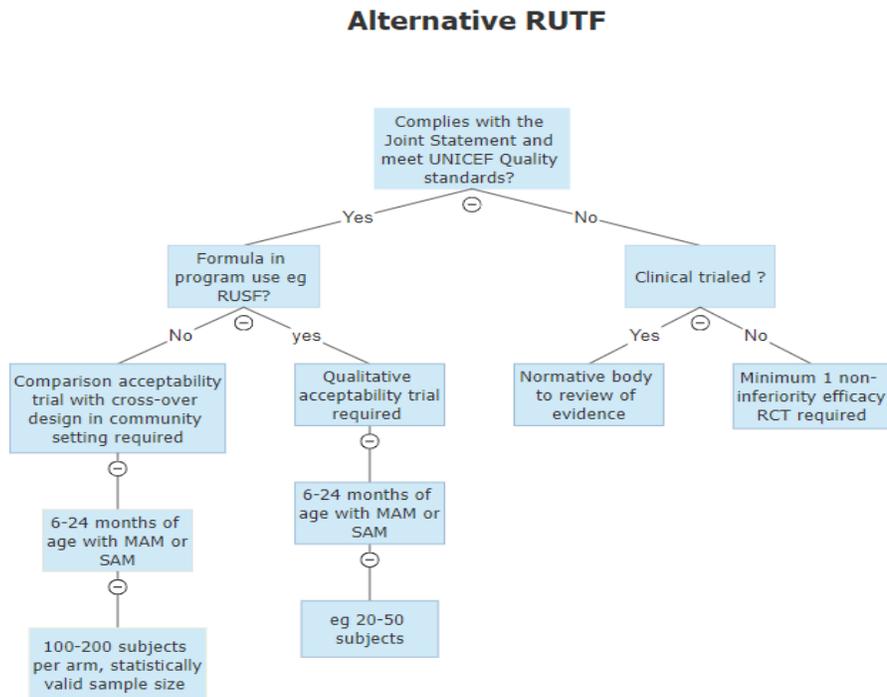
## ACCEPTABILITY TRIAL DESIGN FOR NEW RUTF FORMULATIONS

The following section presents an outline of the discussion of requirements of trial designs for new RUTF formulations:

### Model acceptability trial design

Following discussion in the group, it was agreed that due to RUTF being within the 'Renovation' category and thus complying with the Joint Statement, thereby adhering to nutritional composition, the risks in introducing a new formulation centred on reduced compliance. Due to the list of possibilities of ingredients, organoleptic changes could occur, risking compliance to treatment protocols. Acceptability trials that test compliance would therefore be required for new formulations replacing peanuts prior to procurement. The group also agreed that once there was evidence of one example of an alternative recipe, there would not be a need to do additional studies for same formulation type if it was based on the same bulk ingredient. However, continued product monitoring in the field (as part of programming) to ensure acceptance during scale up was thought to be essential.

The below decision tree was developed to guide decision making for additional evidence creation on acceptability, efficacy or effectiveness, based on compliance with Joint statement:



**Figure 1: decision tree for deciding which kind of evidence is needed for new RUTF formulations.**

The group discussed different options for a study set up and agreed that an acceptability cross-over design was the most appropriate in settings where the standard "Peanut" version has already been used. The studies should be conducted in a non-emergency, community setting with low defaulter rates. Depending on previous use of RUTF in a programming setting, the study population could be either MAM or SAM children 6-59 months as per standard variety. All children should receive the same number of RUTF trial periods for at least 2 x 2 weeks with each product.

## Proposed Acceptability Study Design using a 2x2 cross-over model

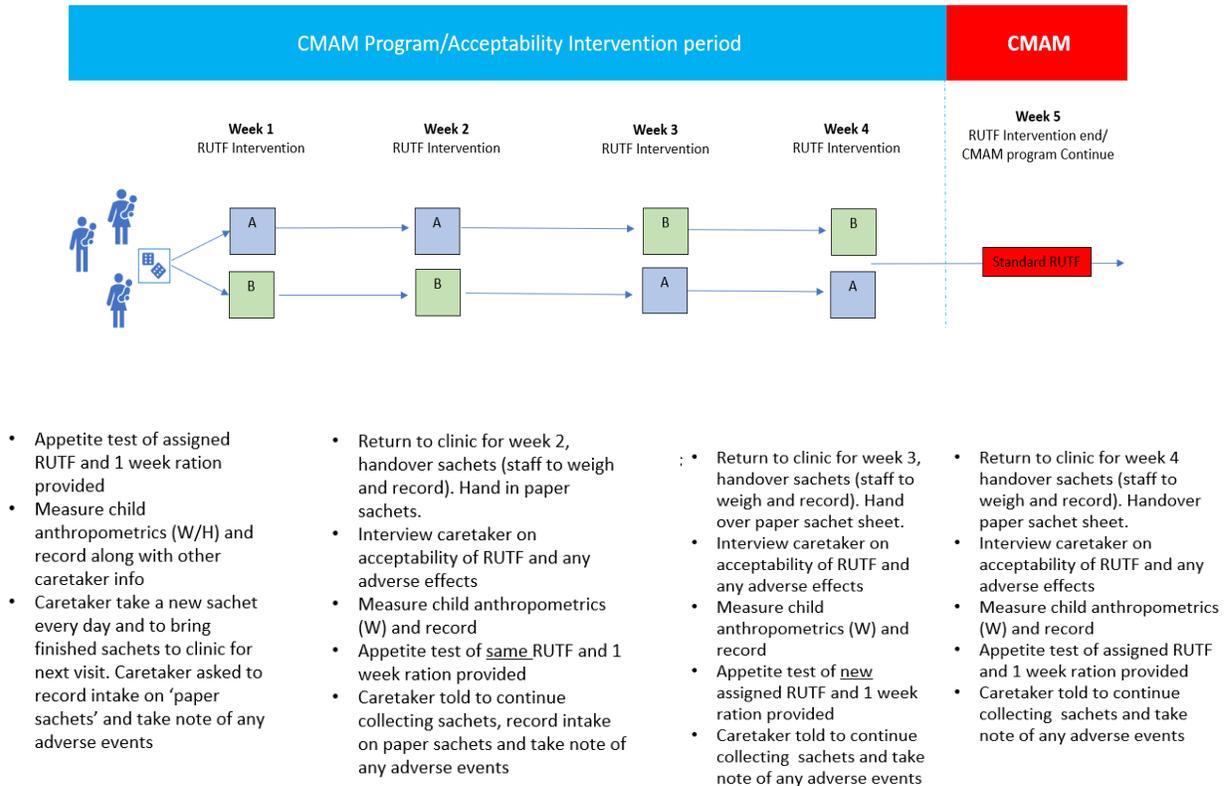


Figure 2: Acceptability Study Design using a 2x2 cross-over model

The cross-over design would cover a 4-week period with a total of 4 visits included for children enrolled in CMAM programmes with SAM without complications (Figure 2 provides an outline of a proposed study). The cross over design will allow for lower numbers in the study as the same subjects are used in the control and active phases of the trials.

The sample size for the cross-over design should be based on the outcome of interest and the group agreed on the following to determine that the product was considered acceptable in the target population.

1. Estimated energy intake per kilo body weight per feed (measured by empty sachets and supported by paper sachets to illustrate quantities ingested over the week)
2. Overall reported acceptance of the product by infants and children from caretakers (including questions on adverse effects such as increase of diarrhoea, flatulence, rash/vomiting associated with the consumption of RUTF)
3. Record if any serious adverse effects (e.g. mortality) supported by medical report

It was recommended by the academic experts, to obtain assistance of a qualified statistician who could help come up with a sample size with the necessary power to be able to detect statistically significant differences in energy intake, and a sample size calculator was shared along with guidance. Using this a sample size of between 100 and 200 children has been suggested to detect differences in intake during the study.

The group also agreed that if the trial was conducted on a specific formulation (e.g. chick pea, soy, maize) by a competent agency following the design example agreed, there would be no need to repeat the trial in multiple settings or countries as children would predictably respond in a similar fashion and the findings could be extrapolated.

## VITAMIN A LEVELS IN RUTF

This session addressed challenges in maintaining Vitamin A levels within the specified current limits (0.8-1.1 mg per 100 grams) throughout the supply chain and shelf life period.

Based on the stability testing reports and feedback from RUTF manufacturers, the maximum Vitamin A limits as the current Vitamin A limits (0.8- 1.1 mg per 100 grams) are too narrow to remain within the specifications during the desired shelf life period.

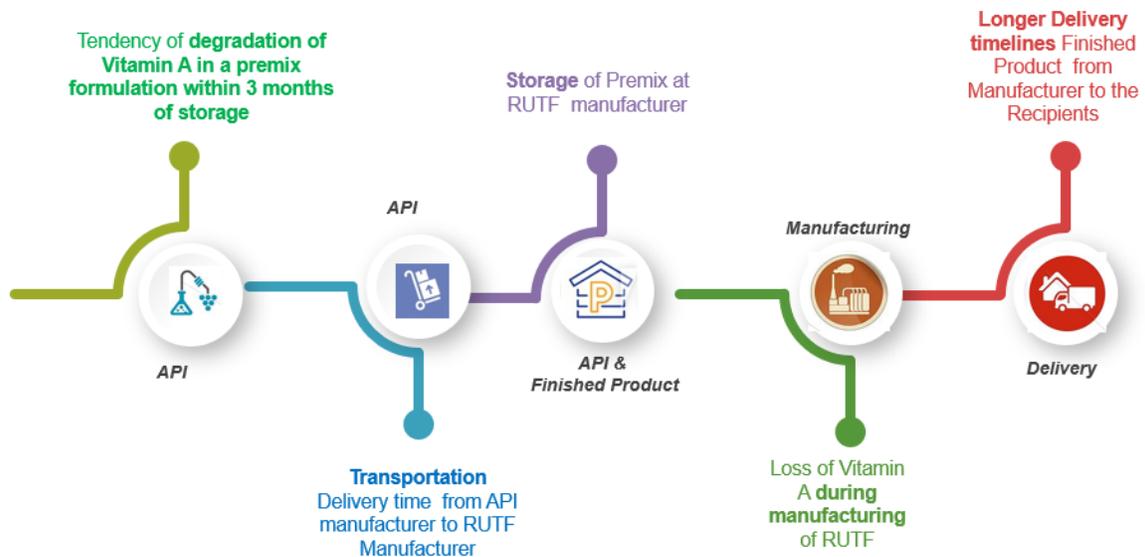
In real life situations, during temperature excursion and storage RUTF's are also at risk of being exposed to conditions over 40°C which may further lead to degradation of vitamin A levels in the product.

### Vitamin A in Vitamin and Mineral Premix

Vitamin A is one of the most chemically unstable vitamins and degrades in the presence of external factors including temperature, oxygen, humidity and light<sup>xv,xvi</sup>. Exposure to these factors leads to degradation during its shelf life period.

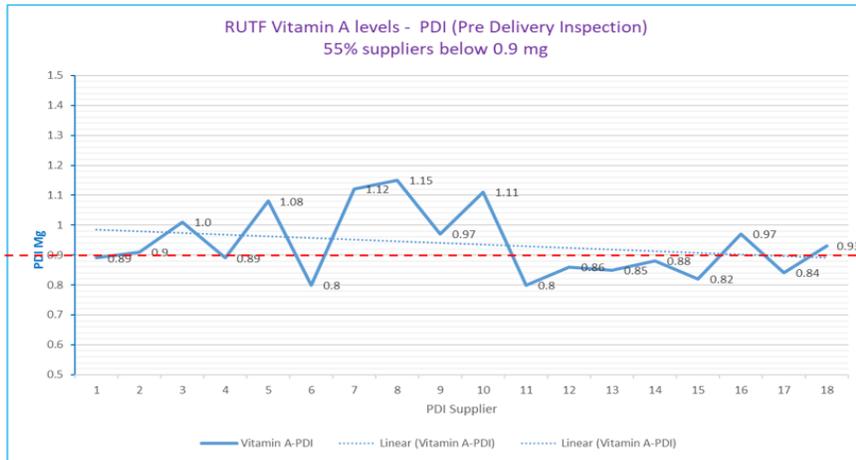
Vitamin A is widely used in RUTF by means of commercial vitamin & mineral premix. It has been reported that in commercial premixes, Vitamin A has a significant loss in activity and around 10-30 % Vitamin A is lost in premix when stored for 3 months<sup>xvii,xviii</sup>.

Vitamin A levels in RUTF are further reduced through the supply chain i.e. during transportation and storage of Premix, RUTF processing (i.e. due to heat generated during processing), temperature excursion & storage of finished product e.g. when stored in containers at ports in Sub-Saharan region and middle east where the temperature may reach above 40°C .

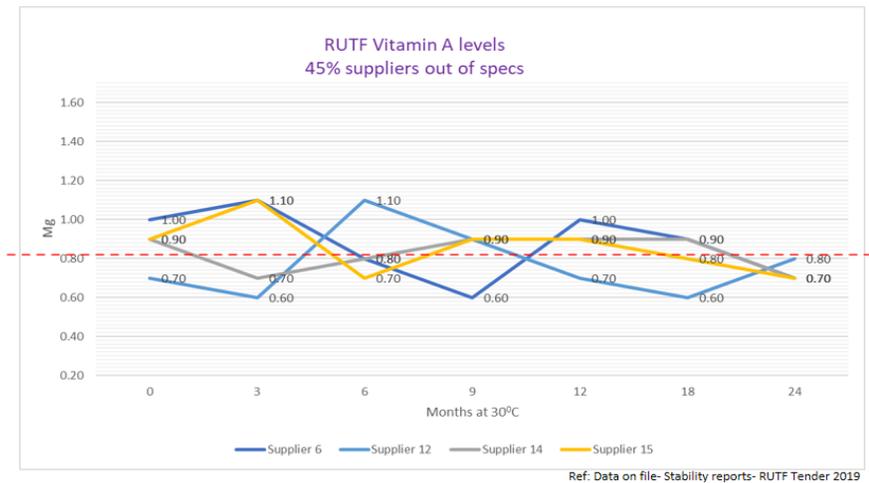


## Vitamin A levels during Pre- Delivery Testing of RUTF

In 2018, vitamin A levels in RUTF were tested during Pre-Delivery Inspections (PDI) and a total of 55% of suppliers had RUTF vitamin A levels below 0.9mg per 100 grams of RUTF in freshly made stock.



Also, on analysis of various RUTF stability study reports during the 24 months period, at 30°C, 45% of RUTF products were found to be out of specifications.



From the 2019 UNICEF tender, stability trend data at 30°C for Vitamin A soft gel capsules containing Vitamin E as anti-oxidant was also used as a comparator to study the degradation pattern of Vitamin A, it shows that in-spite of having high level of anti-oxidant, there is significant degradation at around 18 months.

A 9-year (2010-2018) compiled stability data set shared by a supplier (Nutraset) shows that temperature alone has a huge impact on Vitamin A levels in RUTF. The estimated Vitamin A loss during storage at 30°C is 0,28 mg/100g, i.e. 29% over 24 months, this loss is increased to 55% during storage at 40°C. The technical experts considered the

physical and chemical factors are the causes of low levels of vitamin A in RUTF, such as oxidation due to permeability in the packaging or other oxidative ingredients in the premix such as ferrous sulfate.

The group also discussed standardizing the testing methods for testing vitamin A across the supplier base to reduce the testing variance and enable a uniform interpretation of results across the supplier base.

Historical vitamin A supplementation of 100000 - 200000 IU given to SAM children routinely, provided justification for the expert group to consider increasing the maximum levels of vitamin A in RUTF to ensure that the revised daily vitamin A level of 5000IU (1.5mcg) is achieved. The group discussed the possible revision of vitamin A specification level by an increase of 40-50% for RUTF finished product. Experts advised to build a case to propose increasing the specification levels in the CCNFSDU meeting in 2019 and draft a Conference Room Document (CRD) outlining the discussion points and recommendation from the expert meeting.

The Technical Expert group recommended, UNICEF to provide guidance to suppliers on how to manage premix in their facility, i.e. encourage testing of vitamin A in the Premix - at goods receipt and before using the premix in manufacturing RUTF if stored for more than one month, ensure premix to be stored in cool storage conditions i.e. less than 25° C and advise suppliers to adjust vitamin A levels and or its formulation (eg encapsulated vitamin A) in the premix specification.

From the predelivery inspections reports, it indicates that the initial Vitamin A input levels in the premix used are too low. To address this issue, stipulating that batch release levels of vitamin in RUTF should be not less than 1.1 mcg per 100 grams could also be implemented by procuring agencies.

## CONCLUSION

The technical meeting helped to address various challenges associated with regards to assessment of new formulations of RUTF for procurement agencies and the definition of a new RUTF product. To program new alternative RUTF recipes adhering to nutritional composition within the 'Joint Statement', adequate evidence would be acceptability studies using a two by two factorial design that is adequately powered, and continued product monitoring in the field (as part of programming) to ensure acceptance.

The presence of anti-nutrients in many of the raw materials used in the RUTF formulations needs to be taken into consideration by RUTF manufacturers

Vitamin A levels in RUTF need to maintain a dose of 5000IU(1.5mcg) throughout the shelf life. Suppliers can improve the consistency in delivering this level of vitamin A by monitoring and adjusting the premix for the finished product, and their release limits for the finished product itself.

## Annex 1a: Product documents reviewed during UNICEF Evaluation

1. The product specification for RUTF includes requirements for:
  - a. Raw material / ingredients specifications,
  - b. Microbial and contaminant specifications
  - c. Finished product formulation and its qualities,
  - d. Packaging and labelling specifications
  - e. Storage recommendations and conditions
  - f. Testing requirements and their assay methods of the intermediate and the final products,
  - g. Analytical requirements for the finished product, which need to be included in the Certificate of Analysis (CoA) supplied with each batch.
  - h. Manufacturing standards (i.e. certification requirements) to be adhered to during the manufacture of the product.

## Annex 1b: Components of a specification

2. Specification development work can include the following inputs:
  - a. Existing product specifications
  - b. Existing supplier's specifications
  - c. World Health Organization (WHO) compositional guidelines
  - d. Interagency partners specifications
  - e. Expert opinions for specific criteria of the specification
  - f. Standards, pharmacopoeias and other well recognized references
  - g. Feedback on products from surveys, comments or complaints from UNICEF Program Division (PD) and end users
  - h. Feedback and learnings from peers and partners
  - i. Scientific research and best practice references from relevant journals

**Annex 2. Organoleptic requirements for RUTF alternatives from UNICEFs RUTF Product Specification.**

<b>Texture</b>	Smooth, homogeneous, thick paste, easy to squeeze out of sachet. It should be a uniform paste with no lumps or grittiness, having a small particle size (size < 200 microns) to minimise phase separation, granularity, and oil leaking out of the sachet. The paste should not elicit chewing when consumed by the target population.
<b>Flavour and odour</b>	RUTF paste should have a pleasing sweet, fresh flavour. RUTF paste should be free from foreign odours and flavours such as, (but not limited to) burnt, scorched, rancid, malted, sour, or stale.
<b>Colour</b>	RUTF paste should have cream to light or orangey brown colour. The RUTF paste should not have a dull, grey tinge, or other abnormal cast. It should show no evidence of excessive heating (materially darkened or scorched).

**Annex 3. Questionnaire used for internal organoleptic assessment of RUTF alternative formulations.**

Tasting of RUTF Alternative Formulas												26th July 2019	
Sample	Taste (0-5)					Flavour homogeneity		Granularity (mark one)					
	Sweet	Salty	Bitter	Rancid	Burnt	Yes	No	Smooth	Gritty	Grainy	Granular	Adhesive	
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
13													
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17													
18													
19													
Name: .....													
<i>Smooth: very small or very few particles</i>													
<i>Gritty: small particles present, like icing sugar in butter</i>													
<i>Grainy: particles present, like sugar in butter</i>													
<i>Granular: angular and/or hard particles</i>													
<i>Adhesive: sticks to the teeth</i>													

## Annex 4. List of countries and articles/ studies that represent Renovation category

Annex 4. List of countries and articles/ studies that represent Renovation category					
Location	Ingredients	Study Type	Study design	Study population	Sample size and outcome of interest
Vietnam	Rice, soy, and mung bean on top of standard ingredients	Effectiveness trial	8-week randomized, community-based trial, testing HEBI vs standard RUTF. <i>Phuopng et al., 2014</i>	Children 6–59 months with MAM	150; acceptability, anthropometry (weight gain, MUAC, height)
Bangladesh	1): Rice and lentil 2): Chickpeas. Common ingredients: Dried skimmed milk powder, sugar, soybean oil, and premix.	Acceptability Trial	Clinical trial with cross over design, test the acceptability of 2 local RUTFs compared to the prototype RUTF, Plumpy'Nut. <i>Choudhu et al., 2017</i>	Children 6–59 months with SAM at hospital level	30; acceptability (consumption and velocity)
Bangladesh	Soy-based RUTF (soy protein isolate instead of milk powder)	Efficacy and Acceptability	Double-blind randomized non-inferiority trial. Comparing Soy-based RUTF (S-RUTF) with milk-based RUTF (M-RUTF). <i>Hosseini et al., 2014</i>	Children 6–59 months with SAM, enrolled in the study after completion of stabilization phase of	260 (efficacy, weight gain), 36 (acceptability)
Ethiopia, Ghana, Pakistan and India	Ethiopia: Groundnut, Soybean, oat, milk (acid whey, WPC <sub>34/80</sub> ), canola and palm oil, sugar (20g /100g). Ghana: Soy bean, maize, milk (WPC <sub>34/80</sub> ), canola/coconut/ palm /sunflower oil, sugar 25g/ 100g, cocoa. Pakistan: Almond, lentil, maize, milk (WPC <sub>34</sub> ), canola oil, sugar (24g). India: groundnut, lentil, oat, milk (acid whey, WPC 80), canola/ coconut oil, sugar (18g).	Acceptability Trials	4, two-arm, crossover, site-randomized food acceptability trials to test the acceptability of an alternative RUTF formula (using linear programming) vs standard peanut-based RUTF containing powdered milk. <i>Weber et al., 2016</i>	Children 6–59 months with MAM, healthy children	50 in each study (2x25), acceptability (consumption)
Sri Lanka	RUTF based on soy, lentils and rice	Acceptability Trial	Cross-over design consuming one of three products over a 14 day period, Compared the acceptability of a new ready-to-use therapeutic food (RUTF), against equivalent products (Plumpy'nut® and BPT100). <i>Dibari et al., 2010</i>	3-5 year non-malnourished children	90, acceptability (Meal acceptance (colour, taste, texture, sweetness), energy intake, illnesses).
Bangladesh	Pushti packet (PP) = locally produced treatment for SAM: contained 20 gm of roasted rice powder, 10 gm of roasted lentil powder, 5 gm of molasses and 3 gm of soy bean oil	Operations research, effectiveness study	Operations research to investigate the weight gain of a subsample of malnourished children receiving three different feeding regimens (Pushti Packate, Enhanced Pushti Packet and standard RUTF. <i>Mahfuz et al., 2014</i>	Children 6-59 months with SAM and MAM	161 children, absolute weight gain and rate of weight gain.
Pakistan	Chickpeas, vegetable oils, sugar, skimmed milk powder, vitamins and minerals to meet the specifications of RUSF and LNS-MQ.	Individual, randomised, double-blind controlled clinical non-inferiority trial	Individual, randomised, double-blind controlled clinical non-inferiority trial to compare the effectiveness of a revised formulation of Acha Mum to the standard RUTF. <i>Kureishy et al., 2019. (Unpublished-trial ongoing)</i>	Children aged 6-59 months with uncomplicated SAM	1700 (850x2) for Primary: Recovery; 200 for Secondary outcomes: neurocognitive performance, anthropometric changes, relapse and any
Iran	Chickpea, rice, wheat and barley, named Shadameen in combination with multivitamin/mineral supplement.	Effectiveness trial, randomized clinical trial	Children received either Shamadeen with nutrition counselling or nutrition counselling. <i>Javan et al., 2017</i>	Children 9-24 months with MAM	70, Weight and length gain and recovery rates and adverse events

Continued : Annex 4. List of countries and articles/ studies that represent Renovation category					
India	RUTF Agra local recipe: jaggery (cane sugar), peanut, puffed rice and bengal gram (type of chickpea) to make a total of 100 gm (370kcal/100g). Caretakers watched demonstration and were advised to give 50 gram of this RUTF per day in 3 or more aliquots as dry powder or by making a paste with water or milk.	Hospital based intervention study	Group A (given Family diet only), Group B (given Family diet + RUTF) and Group C (given Family diet + RUTF + Multivitamin preparation containing zincovit drops 5 drops per serving. <i>Sachdeva and Vijayaran, 2014</i>	Children 6-60 months with Protein Energy Malnutrition	125, weight gain, height gain, MUAC gain and rise in level of hemoglobin
India	A diet based on energy dense local foods along with multivitamin-multimineral supplements (initially put on a maintenance diet of about 100 kcal/kg/day, which is slowly increased up to 170-220 kcal/kg/day. A typical diet of a child weighing 7kg consists of 350ml of milk (fortified with oil to increase the energy density), 250g of khichdi (rice and dhal in 2:1 ratio with added oil), 1-2 slices of bread, 2 eggs and a banana, which provides around 170 to 200 kcal/kg/ day and 3 to 4 grams of protein/kg/day. Micronutrients are provided in the form of multivitamin-multimineral syrups	Retrospective cohort study	Retrospective cohort study of 309 children admitted with SAM at an In-patient ward. <i>Mamidi et al., 2010</i>	Children 6-59 months with SAM at hospital level	309, catch up growth in weight (g/kg/day) during each week of hospital stay.
Kenya	Plumpy sup corn formula	Acceptability study	Blinded acceptability test with cross over 2 x 5 days of Maize-based ready-to-use food (RUSF) vs standard RUTF. <i>IPSOS, Nutriset, 2018</i>	Children 12-24 months from food insecure areas with high levels of malnutrition	147, acceptance (general liking and organoleptic properties)
Malawi	Plumpy sup corn formula	Acceptability study	2 week cross-over acceptability study. <i>Ashorn et al., 2018 (Non-Published)</i>	Children 12 to 23 months with MAM	40, Acceptability (compliance with / adherence to the feeding instructions, feasibility for home use)
Ghana	Whey protein, soybeans, peanuts, sorghum	Clinical equivalence trial comparing the alternative with standard RUTF	Clinical equivalence trial using a randomized, double-blinded controlled study set up comparing alternative RUTF with standard RUTF. <i>Hkohlman et al., 2019</i>	Children 6-23 months and 24-59 months with SAM enrolled in study.	1262, Primary: Recovery, Secondary: Rates of weight/MUAC gain, the number of visits before recovery, cost of RUTF per child recovered, and adverse events.

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