Meeting Report: WHO-UNICEF Technical Consultation on ready-to-use therapeutic foods (RUTF)

Improving the availability and cost of RUTF for treating children with severe wasting and/or nutritional oedema

unicef

World Health Organization

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1. Background

In 2020, the United Nations Agencies working on the prevention and treatment of wasting in children released a high-level global action plan (GAP)[1] for child wasting. In this plan, the Food and Agriculture Organization of the United Nations (FAO), the United Nations Office of the High Commissioner for Refugees (UNHCR), the United Nations Children's Fund (UNICEF), the World Food Programme (WFP) and the World Health Organization (WHO) have outlined priority actions to achieve the targets set by the World Health Assembly (WHA) and Sustainable Development Goals (SDG) to reduce the proportion of children suffering from wasting to fewer than 5 per cent by 2025 and fewer than 3 per cent by 2030.[2]

One of the key targets of the GAP is to increase the coverage of treatment for wasting and/or nutritional oedema in children by 50 per cent by 2025. To reach this target, key commodities, including RUTF, should be of high quality and routinely available at an affordable price at every contact point for the treatment of these conditions.

In 2007, WHO, WFP, the United Nations System Standing Committee on Nutrition (UNSSCN) and UNICEF released a joint statement on community-based management of severe acute malnutrition, which states that at least 50 per cent of the proteins in RUTF should come from dairy products.[3] Recently, alternative RUTF formulations with different sources of protein have been tested in several trials. One of the aims of these alternative RUTF formulations is to reduce the production cost by partially, or fully, replacing dairy protein with cheaper and/or locally available options. Reducing the cost of RUTF would increase its availability and improve treatment coverage.

In July 2021, WHO assembled a guideline development group (GDG) to evaluate the evidence on the non-dairy and reduced-dairy RUTF formulations. The GDG discussed the evidence from the **systematic review** commissioned for this guideline and concluded that the efficacy outcomes favoured the standard RUTF, which contain at least 50 per cent of protein from dairy products. However, the GDG acknowledged that, since up to 30 per cent of the cost of RUTF is due to the dairy content, replacing dairy with cheaper alternatives is a good strategy to reduce the overall cost of RUTF. Nevertheless, despite the potential for a greater price reduction, replacing the dairy content of RUTF with alternative sources of protein has demonstrated only modest savings to date (up to a 5 per cent cost reduction of the global weighted average price, according to public tendering exercises).

The GDG therefore recommended further research to demonstrate not only the efficacy, but also the costs, resource use, and cost-effectiveness, as well as the acceptability and feasibility, of these alternative RUTF formulations.

Following publication of the **WHO guideline on the dairy content of RUTF**, in November 2021, WHO and UNICEF convened a two-day technical consultation to identify solutions on RUTF formulations that will have the most impact on improving the availability and reducing the cost of RUTF, and on how to generate the evidence needed to support these solutions.

[1] World Health Organization, *Global Action Plan on Child Wasting: a framework for action to accelerate progress in preventing and managing child wasting and the achievement of the Sustainable Development Goals*, WHO, Geneva, March 2020.
[2] World Health Organization, United Nations Children's Fund, *The extension of the 2025 Maternal, Infant and Young Child nutrition targets to 2030*, Discussion paper, WHO and UNICEF, 13 June 2019.
[3] World Health Organization et al., *Community-based management of severe acute malnutrition. A Joint Statement by the World Health Organization, the World Food Programme, the United Nations System Standing Committee on Nutrition and the United Nations Children's Fund*, WHO, Geneva, May 2007.

2. Meeting objectives

The objectives of the meeting were to discuss barriers and solutions to reduce the cost and improve the availability of RUTF and the way forward for generating evidence for the development of new RUTF formulations, including defining:

- a WHO process for assessing emerging evidence for global guidelines
- the type of evidence required for different types of RUTF formulations
- the appropriate methods for collecting the evidence across different contexts.

3. Summary of the presentations and discussions

Presentations and discussions from the technical consultation are summarized in the subsections below.

3.1 Cost of programming: the big picture

Lani Trenouth (UNICEF) presented the data on the costs of treating children with severe wasting and/or nutritional oedema

It is often assumed that RUTF is the primary cost driver in an outpatient service delivery model and that reducing the cost of RUTF will yield significant improvements in cost-efficiency, yet the median contribution of cost from product supplies for an integrated management of acute malnutrition (IMAM) programme is 23 per cent (4–43 per cent). Thus, total service delivery cost-savings with a lower unit cost of RUTF may be less than anticipated. Literature reviews show that the cost of treating a child with severe wasting and/or nutritional oedema varies widely, from $27 to $520 per child admitted for treatment; and $152 to $1491 per child recovered from severe wasting and/or nutritional oedema. The wide range in cost estimates reflects programmatic and contextual differences but also the differences in costing methods. Greater standardization of these methods is required to improve the reliability and comparability of cost estimates of treatment and recovery from wasting and/or nutritional oedema.

A combination of reducing the unit cost and the total amount of RUTF provided would yield a greater reduction in the cost, with the proviso that a reduced dosage is non-inferior in terms of effectiveness and other patient safety aspects. More robust data is needed to confirm this.

Key message: RUTF is an important cost, but not the major cost in programmes for the treatment of wasting and/or nutritional oedema; existing literature on total programme cost estimates are variable and not comparable across settings, which limits their utility in estimating potential cost-savings of modifications to the unit cost or dosage of RUTF. Reducing the cost of RUTF, combined with reducing the dose of RUTF may have greater impact in improving availability of RUTF but these actions would need the support of robust data.

3.2 RUTF market influences and UNICEF market approach

Jan Debyser (UNICEF) gave a presentation on the RUTF market overview and influences

UNICEF procurement of RUTF increased exponentially from a few hundred tons in the early 2000s to more than 50,000 (about 3.6 million cartons) a decade later. The industry struggled initially to meet the rapid increase in demand following the endorsement of the use of RUTF for community-based treatment in the 2007 United Nations Joint Statement[1] and the growing use of RUTF for emergency responses. Market shaping led to an expansion of production capacity and development of a local supplier base close to the needs, supported by improved standards and more robust quality-assurance systems. Today's global RUTF capacity of more than 20 manufacturers in four continents is estimated at around 300 000 tons.

[1] Ibid.

UNICEF procures an estimated three quarters of globally funded demand for RUTF; 20 countries account for 90 per cent of UNICEF RUTF demand, of which two thirds are from Africa.

The global weighted average price of RUTF reduced by more than 20 per cent over the last 10 years. RUTF suppliers operate on thin operating costs and profits, with raw and packaging materials making up 75 per cent of the finished product cost. Key raw materials are volatile agricultural commodities with limited market influencing potential. Global staple commodity indexes have a dominant impact on the price of RUTF.

Locally procured RUTF is often more expensive than imported RUTF, but this price difference is minimized when landed product prices are compared (including the costs for freight and clearing Customs). Locally procured RUTF offer supply chain efficiencies and better lead times due to the proximity of the manufacturer to the beneficiaries and they also facilitate government endorsement and acceptance into health systems due to the downstream economic and social development benefits. However, local suppliers often face unfavourable tax environments, and may have limited access to investment capital and affordable financing. Moreover, several suppliers in Africa need to use offshore laboratories for their product testing, which can add significant lead times to product releases.

Some of the important factors that contribute to a healthy and sustainable RUTF market are:

- predictable long-term funding
- supply meeting the demand with a quality, affordable, timely and acceptable product
- a geographically well-spread supplier base close to the needs
- a competitive and resilient supplier base with a diversified client base
- the ability to leverage savings on raw material purchase across a product portfolio
- policies and legislation that support local production.

Key message: Locally procured RUTF ensures that the product is closer to the end users, is more acceptable, and has downstream economic and social development benefits. Unfavourable tax environments, access to capital, and reliable quality controls are some of the challenges that local producers face. Locally procured RUTF is often more expensive than imported RUTF, but this price difference is minimized when landed product prices are compared. Market shaping over the last 15 years has resulted in a competitive RUTF supplier base close to where the needs are, with sufficient capacity to meet (funded) demand.

Pricing data for UNICEF procured nutrition commodities can be found at
www.unicef.org/supply/pricing-data

3.3 Ingredients in RUTF and their associated costs

Alison Fleet and Liang Zhao (both UNICEF) presented facts on RUTF ingredients and their associated costs

The four main costs of RUTF are dairy (37 per cent), peanuts (29 per cent), oil (11 per cent), packaging (9 per cent), premix (6 per cent) sugar (5 per cent) and other costs (3 per cent). Raw material price volatility is a significant risk exposure for RUTF suppliers and increases the cost by $5–$10 per carton. Over 10 years, pricing swings of up to 50 per cent for peanuts, 75 per cent for milk, 60 per cent for vegetable oil and 90 per cent for sugar have been reported. Moreover, there is a wide range of applied taxes across different countries to manufacture and procure RUTF, increasing the weighted average price (WAP) by an estimated 2.66 per cent.

Key message: RUTF pricing is susceptible to market dynamics, particularly raw material markets and a variable taxation environment.

3.4 UNICEF Quality standards: Quality assurance of RUTF

Peter Svarrer Jakobsen (UNICEF) presented information on the quality assurance processes for RUTF

All products procured by UNICEF, regardless of their production facility location, are required to meet strict standards for food safety and quality. The major food safety risk in RUTF production is contamination with the bacteria *Salmonella*. The supplier requirements for RUTF production have changed over the years and most RUTF is now produced in an industrial facility to ensure microbial control and consistent quality of high-volume output.

The quality audit follows the format of the Inter-agency Specialized Food Manufacturers Quality Questionnaire, and this questionnaire is shared with suppliers to prepare for the audit. Quality audits use references from the International Food Standards contained in the Codex Alimentarius, 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).

New RUTF formulations should be compliant with **WHO guidelines** and the **Codex guideline for RUTF**, meet specification requirements of the Inter-agency Group for Specialized Nutritious Food Products,[1,2,3] and be produced in a facility that meets inter-agency quality requirements.

Key message: RUTF is now produced in industrial facilities to ensure microbial control and consistent quality of high-volume output. All suppliers are expected to follow WHO and Codex guidelines and standards and are regularly checked by one of the inspectors from the inter-agency group.

3.5 Alternative RUTF formulations: Categories of products

Alison Fleet and Jan Debyser (both UNICEF) presented the next generation of RUTF products.

UNICEF has categorized the alternative formulations that have been reported by studies into three groups: the Renovation, Innovation and Novel categories.

The renovation category uses different legumes, cereals and seeds that replace peanuts. These formulations follow the technical annex in the 2007 United Nations Joint Statement and the **Codex guideline for RUTF**. The Innovation category replaces milk with another animal protein source. The Novel category replaces milk with plant-based proteins or added amino acids with increased micronutrients. These formulations do not follow the technical annex in the 2007 United Nations Joint Statement[5] or the **WHO guidelines**.

Chickpea and soy ingredients were present in the majority of offers during UNICEF's request for tenders in 2019–2021. Prices for Renovation formulations submitted to UNICEF were 3.67 per cent cheaper for offshore suppliers and 6.7 per cent cheaper for local suppliers. Novel formulations are 1.79 per cent

[1] The International Inter-Agency Working Group for Specialized Nutritious Food Products (SNFPs) is a group that promotes appropriate formulations, modifications, and use of specialized nutrition food products in a manner that complies with international standards and is consistent with guidance from normative bodies on nutritional value and food safety, also taking into account advances in science, including product-related research and development, operational needs of agencies, and empirical understanding of costs and effectiveness. Member organizations include WFP, UNICEF, WHO, FAO, Doctors Without Borders (MSF), The International Committee of the Red Cross (ICRC), Action Against Hunger (ACF), The United States Agency for International Development (USAID) and The United States Department of Agriculture (USDA)

[2] Inter-Agency Working Group For Specialized Nutritious Food Products, 'Terms Of Reference', October 2016, <**https://foodaidquality.nutrition.tufts.edu/sites/default/files/uploads/Inter-agency%20TOR_FINAL%20v1%20%2813%20Oct%202016%29.pdf**>.

[3] United States Agency for International Development et al., International Inter-Agency Working Group for Specialized Nutritious Food Products, 13th Inter-Agency Harmonization Meeting, May 26–28, 2020, Communiqué, <**https://pdf.usaid.gov/pdf_docs/PA00XC2C.pdf**>.

cheaper for offshore producers and 15 per cent cheaper for local suppliers; the disparity being due to a higher initial WAP for the standard product from local sources.

Table 1: Comparison of Renovation and Novel categories

Tender condition that products with alternative ingredients/recipes are offered at a lower price than the standard peanut/milk version offered by the same manufacturer

When only considering valid and comparable (base) offers: price reduction per carton ranges from 1.79% to 15.00%, with below medians.

Renovation (seeds, cereals or legumes replace peanuts)		**Novel (no milk, added amino acids and different Zn, Fe and Vit C)**	
Off-shore	Local	Off-shore	Local
% Median Price reduction	% Median Price reduction	% Median Price reduction	% Median Price reduction
3.67 % (all) 3.23 % (soy) 2.88 % (chick peas)	6.70 % (all) n/a (soy) 8.35 % (chick peas) 4.55% (oats)	1.79 %	15.00 %

Key message: Alternative RUTF products have the potential to reduce the cost of RUTF between 1.79 per cent and 15 per cent (as of 2022) depending on the location of the supplier and category of next-generation RUTF.

3.6 Codex guideline for RUTF

Nolene Naicker (Codex representative, Government of South Africa) gave a presentation on the upcoming Codex guideline on RUTF

The 2007 United Nations Joint Statement[5] contains a technical annex with general information regarding RUTF. This annex does not stipulate any particular ingredients to use in RUTF except the guidance that at least 50 per cent of protein should come from dairy sources. As the 2007 United Nations Joint Statement's main purpose was to outline the use of RUTF in the community-based management of severe wasting and/or nutritional oedema, the technical annex provides only brief guidance regarding the nutritional composition of RUTF.

In 2014, meeting discussions began to develop a **Codex guideline for RUTF**. Since then, several consultations and discussions have occurred. During a meeting in 2019, the Member States agreed to include a protein quality score after FAO commissioned a review of the requirements of protein for children with severe wasting and/or nutritional oedema.[1] A protein digestibility corrected amino acid score (PDCAAS) of more than 90 was deemed adequate to facilitate recovery. The FAO report did not specifically state that dairy protein was needed to achieve this score, however the Codex guideline for RUTF does specifically mention that high-quality protein will be achieved with RUTF formulations containing a minimum of 50 per cent of protein coming from milk products.

Key message: The **Codex guideline for RUTF** is now published and builds on the 2007 United Nations Joint Statement to provide specific guidance on the ingredients, quality standards and food safety aspects for the manufacture of an efficacious RUTF product. The guideline provides updated Codex standards and references relevant to reduce food safety risks such as microbiological and contaminant hazards.

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[1] Food and Agriculture Organization of the United Nations, *Protein quality assessment in follow-up formula for young children and ready to use therapeutic foods*, Report of the FAO Expert Working Group, Rome, 6–9 November 2017, FAO, Rome.

3.7 Systematic review results: Iron and essential fatty acids in RUTF

Jaden Bendabenda (WHO) presented findings of the systematic reviews that were commissioned to provide evidence for the Codex guideline for RUTF, focusing on the content of essential fatty acids and iron in RUTF

3.7.1 Essential fatty acids content in RUTF

Infants and young children need long chain polyunsaturated fatty acids (LCPUFA) for the development of the brain and the nervous system. Essential fatty acids (EFA) such as linoleic acid (LA, 18:2 omega-6) and alpha linolenic acid (ALA, 18:3 omega-3) cannot be synthesized by the body and must be supplied in the diet and, hence, are included in the nutritional composition for the Codex Guideline for RUTF.

Emerging evidence suggests that RUTF formulations that follow the 2007 United Nations Joint Statement do not have LCPUFA profiles that can support optimal brain development, and that alternative LCPUFA profiles in RUTF could be used to promote brain and nervous system development.

As part of the work for the Codex guideline for RUTF, WHO commissioned a systematic review to evaluate the scientific evidence regarding the fatty acid profiles needed to improve and harmonize the fatty acid composition in RUTF.

The systematic review question was framed in the following PICO (population, intervention, comparison and outcomes) format:

Does provision of RUTF with fatty acid profiles that are different from the specifications in the technical annex of the 2007 United Nations Joint Statement improve outcomes such as neurodevelopment in children aged 6 months or older recovering from severe wasting and/or nutritional oedema?

The systematic review[1] identified three eligible randomized controlled trials (RCT)[2,3,4] that were eligible. Only one trial (Stephenson et al., 2022) assessed neurodevelopment which was the primary outcome of the review. The trial reported that children aged 6–59 months receiving RUTF with high oleic peanuts with added docosahexaenoic acid (DHA-HO-RUTF) had higher developmental scores in some, but not all outcomes. The review concluded that DHA may confer some benefits to neurodevelopment but also highlighted the lack of data to support recommending specific amounts (or ranges) of ALA and LA in RUTF. These data should ideally come from dose-response studies.

On costs and resource implications of this change (i.e., increasing the ALA content and reducing the LA content) a rapid survey of UNICEF's RUTF suppliers' base showed that the proposed changes may be feasible for most of the suppliers. According to this survey, the theoretical cost change was estimated to be between 0–20 per cent depending on the supplier location and access to ingredients. Only the Stephenson trial reported on the costs of this change.[5] In this trial, it was estimated that high oleic vegetable oils could cost about 10 per cent more than the traditional vegetable oils, which could result in an increase in the cost of RUTF.

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1 World Health Organization, *WHO summary on the available evidence for the essential fatty acid profiles in ready-to-use therapeutic foods for treating children with severe wasting*, <**www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-720-42%252FLinks%252FWHO_summary_on_EFA_in_RUTF.pdf**>, accessed 5 June 2023.

2 Jones, Kelsey, D., et al.,. 'Ready-to-use therapeutic food with elevated n-3 polyunsaturated fatty acid content, with or without fish oil, to treat severe acute malnutrition: a randomized controlled trial', *BMC Medicine*, April 2015.

3 Hsieh, Ji-Cheng, et al., 'High oleic ready-to-use therapeutic food maintains docosahexaenoic acid status in severe malnutrition: a randomized, blinded trial', *Journal of Paediatric Gastroenterology and Nutrition*, July 2015.

4 Stephenson, Kevin et al., 'Low linoleic acid foods with added DHA given to Malawian children with severe acute malnutrition improve cognition: a randomized, triple-blinded, controlled clinical trial', *The American Journal of Clinical Nutrition*, May 2022.

5 Ibid.

All three trials reported significant changes in plasma fatty acid profiles associated with the improved LCPUFA profiles.

However, in finalizing the text for the Codex Guideline for RUTF, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) agreed to change the ALA and LA content in RUTF considering the potential benefits to neurodevelopment of children recovering from severe wasting and/or nutritional oedema.[1]

Key message: Adding DHA to or increasing the ALA and reducing the LA content in, RUTF may confer some benefits to the neurodevelopment of children recovering from severe wasting and/or nutritional oedema. However, the evidence is not strong enough to conclude that this change will have substantial benefits or harms. There is also not enough evidence to determine the optimal amount of ALA and LA that should be in RUTF. The cost implications of this change are not yet certain; therefore decision makers will need to closely monitor the cost of RUTF when implementing this change.

3.7.2 Iron content in RUTF

The standard RUTF formulation is designed to provide about 1.9 mg iron per 100 kcal but emerging evidence suggests that this dose is not adequate to meet the requirements of a child recovering from severe wasting and/or nutritional oedema. In children recovering from severe wasting and/or nutritional oedema, the daily requirements for iron may be increased to meet the demand for rapid growth; the bioavailability of iron may also be reduced due to malabsorption. In addition, studies have consistently reported high prevalence rates of anaemia (40–90 per cent) in children with severe wasting and/or nutritional oedema which persist even after the children have achieved anthropometric recovery.

As part of the work for the Codex guideline for RUTF, WHO commissioned a systematic review to evaluate the scientific evidence to determine the optimal content of iron in RUTF.

The systematic review question was framed in the following PICO format:

In children aged 6 months or older, with uncomplicated severe wasting and/or nutritional oedema, does RUTF with higher iron content, compared with standard RUTF, improve outcomes such as blood haemoglobin (Hb), and recovery from iron-deficiency anaemia (IDA)?

The **systematic review** identified three eligible RCTs.[2,3,4] All three trials showed that RUTF products with higher iron content resulted in increased blood Hb concentration and reduced the prevalence of IDA compared to standard RUTF. There was also a potential increase in all-cause mortality for children receiving RUTF with higher iron content compared to those receiving standard RUTF, although this was not statistically significant.

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[1] Codex Alimentarius, International Food Standards, *CCNFSDU42 Codex Committee on Nutrition and Foods for Special Dietary Uses 19/11/2021 – 01/12/2021/ Virtual*, <**www.fao.org/fao-who-codexalimentarius/meetings/detail/en/?meeting=CCNFSDU&session=42**>, accessed 6 June 2023.

[2] Irena, Abel, H., et al., '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', *Maternal & Child Nutrition*, December 2015.

[3] Bahwere, Paluku, et al,. 'Soya, maize, and sorghum-based ready-to-use therapeutic food with amino acid is as efficacious as the standard milk and peanut paste-based formulation for the treatment of severe acute malnutrition in children: A noninferiority individually randomized controlled efficacy clinical trial in Malawi', *The American Journal of Clinical Nutrition*, Vol. 106, No. 4, October 2017 pp. 1100–1112.

[4] Akomo, Peter, et al., 'Soya, maize and sorghum ready-to-use therapeutic foods are more effective in correcting anaemia and iron deficiency than the standard ready-to-use therapeutic food: Randomized controlled trial', *BMC Public Health*, June 2019.

Key message: It could be argued that the iron content in RUTF should be increased because of:

- the rapid growth rate in children with severe wasting increases the need for iron
- the high prevalence of anaemia in children with severe wasting
- the evidence that provision of RUTFs with higher iron content resulted in improvements in Hb status and reduction of IDA.

However, the available evidence is not adequate to determine the optimal content of iron in RUTF. Well-designed, large RCTs (ideally demonstrating a dose-response relationship) are urgently needed to answer this question.

3.8 Impact of new formulations on micronutrient bioavailability

Maria Nieves Garcia-Casal (WHO) gave a presentation on how changes to the ingredients in RUTF may affect the bioavailability of micronutrients

The micronutrient bioavailability of RUTF is determined based on the following considerations:

- the nutritional composition of RUTF
- the interaction between different nutrients and the food matrix
- the safety of the nutrient.

When selecting which compound(s) to use, the properties of each micronutrient should be considered. For example, iron can be highly reactive when combined with other ingredients due to its ability to catalyse oxidative reactions. Some foods and compounds also affect iron absorption (i.e., are enhancers or inhibitors). When assessing the impact of changing the formulation on health outcomes, it is important to consider the problem of micronutrient deficiencies in the target population (i.e., children with severe wasting and/or nutritional oedema), and the prevalence and control measures of other conditions that can interact with micronutrients (e.g., infections such as malaria when considering iron).

RUTF transport and storage temperature conditions also have an impact on the level of nutrients over time. To maintain the desired level of micronutrients in the final product, it is necessary to keep transport and storage conditions below 30 C.

Key message: Changing the ingredients of the RUTF formulation will also change the micronutrient balance, the bioavailability of the nutrients, and organoleptic properties of RUTF.

3.9 Antinutrients in RUTF

Monica Rios (UNICEF) spoke on the presence of antinutrients in RUTF

Antinutrients are compounds, usually produced in plants, that cause a decrease in the efficiency of nutrient absorption. Many of the antinutrients are found in the seed coats, which are removed during production processes such as peeling and milling. Those found as part of a seed can be decreased or inactivated through thermal, enzymatic or fermentation treatments that are part of the usual transformation process to make the seeds more palatable. At present there are no maximum levels defined for antinutrients for RUTF.

UNICEF recently tested a total of 27 samples of RUTF to determine their levels of lectins, trypsin inhibitor and phytic acid. Of these, 21 were peanut-based RUTF, 4 were soy-based RUTF and 2 were chickpea-based RUTF. The levels of lectin, trypsin inhibitor, and phytic acid were all at, or below, the

level of detection, except for one soy sample which was considered an outlier. This sample showed levels higher than the others, but not at a level that would cause concern.

Key message: Testing of finished product RUTF demonstrated very low levels of the known antinutrients' lectins, trypsin inhibitors, and phytic acid in products based on peanuts, soy and chickpeas. It appears that the prior processing of RUTF ingredients, in combination with the initial low level of these antinutrients, minimizes the risk of absorption inhibition in the formulas.

3.10 Defining WHO process for assessing evidence for global guidelines

Jaden Bendabenda (WHO) spoke about the processes WHO follows to formulate guidelines

The WHO guideline development process follows the steps outlined in the *Handbook for guideline development,*[1] which states that global guidelines should:

- meet the highest quality standards for evidence-based guidelines
- be based on high-quality systematic reviews of all relevant evidence
- use GRADE (Grading of Recommendations, Assessment, Development and Evaluation),[2] which provides an explicit approach to assessing the certainty of the evidence across studies and translating evidence to recommendations
- incorporate multiple processes to minimize bias and optimize usability
- incorporate transparency in all judgments and decision-making processes.

The Guideline Development Group (GDG) is responsible for formulating the recommendations based on the available evidence and is thus central to the process. GDG members are carefully selected to ensure the technical skills, diverse perspectives and geographic representation needed. The members are also required to declare any conflicts of interest and do not receive any financial compensation.

GDG members follow the GRADE process and make a recommendation by considering evidence from all nine domains of the evidence-to-decision framework namely:

- the evidence of effectiveness
- the evidence of any potential harms
- the balance between desirable and undesirable effects
- preferences and values
- equity, gender and human rights
- feasibility
- acceptability
- costs and resource use
- overall certainty of evidence.

In the case of the **WHO guideline on the dairy content of RUTF**, there were 11 GDG members drawn from all WHO geographical regions. The guideline development group reviewed the evidence from two systematic reviews of the effectiveness outcomes and the qualitative outcomes. The evidence for

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[1] World Health Organization, *WHO handbook for guideline development*, 2nd Edition, December 2014, <**www.who.int/publications/i/item/9789241548960**>.

[2] GRADEpro, 'Publications about the GRADE approach', <**www.gradepro.org/resources**>, accessed 6 June 2023.

effectiveness was derived from six trials.[1,2,3,4,5,6] The guideline development group concluded that using non-dairy or reduced-dairy formulations of RUTF would potentially result in lower recovery rates and lower weight gain. There was also uncertainty about the cost-savings associated with alternative RUTF formulations, due to a lack of published data.

The guideline development group therefore determined that the available evidence was not adequate to change the existing recommendation that RUTF should contain 50 per cent protein sourced from dairy products but noted the potential of these alternative RUTF formulations if more evidence on the effectiveness, costs, resource use, and cost-effectiveness is published.

Key message: The GDG uses the GRADE approach to formulate recommendations. This includes the evaluation not only of effectiveness outcomes, but also other domains of the evidence-to-decision framework such as acceptability, feasibility and cost. There is the potential for alternative formulations to be used in routine programmes if more evidence on effectiveness, costs, resource use, cost-effectiveness, acceptability, and feasibility is generated. High-quality research on these formulations is encouraged to inform the next guideline update.

3.11 Summary of the Technical Expert Meeting on RUTF, 2019, Copenhagen report

Alison Fleet (UNCEF) presented details of the summary of the previous meeting to discuss new formulations that took place in 2019

A two-day technical meeting was held to enable discussion on what kind of information would be needed for public procuring agencies to assess new formulations of RUTF. UNICEF coordinated the meeting with experts from a diverse background, including representation from WHO, FAO, WFP, Doctors Without Borders (MSF), the United States Agency for International Development (USAID), Copenhagen University and a representative from the South African National Department of Health. The purpose of the meeting was to hear expert opinion on the development of quality standards, discuss evidence requirements for alternative recipes of RUTF that comply with the product technical annex of the "Joint Statement." The discussion of this technical meeting centred on RUTF products that use cereals, seeds or legumes as alternatives to peanuts while complying with the specification on the minimal content of dairy proteins within the reference 2007 United Nations Joint Statement. The meeting included discussions on the possible raw materials that could be used in RUTF alternative formulations, their relative content of antinutrients and the management of these factors in the finished product.

A working definition of a new RUTF product was developed in the meeting. To enable products to be ready for use in nutrition programmes, the group discussed the criteria for assessment and the need for evidence of effectiveness of the formulation after hearing summaries of the current scientific literature on formulations of RUTF. The group identified that the main risk with new formulas that met the Joint Statement nutritional composition was that the organoleptic properties of the new formulas would lead children to consume less than the amount they needed for recovery. Thus, the group agreed that

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[1] Oakley, Eleanor 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', *Journal of Nutrition*, Vol. 140, No. 12, December 2010, pp. 2248–2252.
[2] Bahwere Paluku et al., 'Soya, maize, and sorghum-based ready-to-use therapeutic food'.
[3] Irena Abel, H., et al., 'Comparison of the effectiveness of a milk-free soy-maize-sorghum-based ready-to-use therapeutic food'.
[4] Bahwere Paluku et al., 'Cereals and pulse-based ready-to-use therapeutic food as an alternative to the standard milk- and peanut paste-based formulation for treating severe acute malnutrition: a noninferiority, individually randomized controlled efficacy clinical trial', *The American Journal of Clinical Nutrition*, Vol. 103, No. 4, April 2016, pp. 1145–1161.
[5] Hossain Md Iqbal, et al., Acceptability and efficacy of ready-to-use therapeutic food using soy protein isolate in under-5 children suffering from severe acute malnutrition in Bangladesh: a double-blind randomized non-inferiority trial, *European Journal of Nutrition*, Vol. 59, No. 3, April 2020, pp. 1149–1161.
[6] Sigh Sanne, et al., 'Effectiveness of a locally produced, fish-based food product on weight gain among Cambodian children in the treatment of acute malnutrition: a randomized controlled trial', *Nutrients*, Vol. 10, No. 7, July 2018, p. 909.

acceptability trials would be adequate to test new formulas, provided that they could measure the difference in consumption between the standard and the new formulas, and that adequate monitoring of the alternative RUTF was implemented to track any deviations from expected programme outcomes or longer-term adverse effects.

The experts proposed a two-by-two crossover acceptability trial design to detect differences in the alternative versus the standard formulation. The main outcome of interest would be the RUTF consumption over the designated study period by the target population, and any adverse events.

Key message: The expert group reached consensus on the three main identified factors that may affect the compliance of the alternative formulations. These are the:

- quality of the products
- level of antinutrients
- change in organoleptic profile.

Consequently, new products must be evaluated for quality, antinutrients and then trialled in a well-designed acceptability study to assess consumption over several weeks. For alternative formulas that did not meet the United Nations Joint Statement nutritional composition, an efficacy trial to demonstrate effectiveness was recommended. See the link to the meeting report here: **www.unicef.org/supply/documents/report-expert-meeting-ready-use-therapeutic-foods-rutf**.

4. Discussion

4.1 Best practice in trial design for new formulas of RUTF

This was a group discussion in which all meeting participants contributed their views on the way forward for generating research on RUTF formulations. Participants were split in two groups of 35 participants, with a balance of researchers and programme implementers in each group. The discussions were guided by two predefined key questions:

a. For new RUTF formulations that *follow* the specification in the technical annex of the 2007 United Nations Joint Statement:

i. Are efficacy trials required or are acceptability trials enough?
ii. If efficacy trials are required, how should efficacy be established?

Participants in the first group proposed that efficacy trials should be required before introducing any new RUTF formulations (including those that follow the 2007 United Nations Joint Statement) for the following reasons:

- Acceptability trials help to determine if children are consuming a new formulation but, alone, cannot provide adequate information about the effectiveness and safety of giving new formulation to children with severe wasting and/or nutritional oedema.
- There is uncertainty regarding how the new ingredients will affect the bioavailability and interactions between the different nutrients in the new formulations.

The group also proposed that, when designing efficacy trials, there is a need for consensus on the primary outcomes across the trials to help comparability during meta-analyses. There is also a need to review the biological usefulness of weight gain as a primary outcome for efficacy trials on RUTF since anthropometric recovery in children with wasting and/or nutritional oedema is now defined by specific weight-for-height and mid-upper arm circumference measurement cut-offs. In addition, the quality of tissue accretion is more important for sustained recovery than rapid weight gain.

Participants in the second group proposed that acceptability trials only are adequate for new RUTF formulations that follow the 2007 UN Joint Statement, for the following reasons:

- There is a need to be pragmatic and find a middle ground by balancing the need for best evidence while, at the same time, not causing unnecessary delays in identifying new, cost- effective RUTF formulations. Therefore, RUTF formulations that are compliant with the technical annex in the 2007 United Nations Joint Statement, the **WHO guidelines** and **Codex guideline for RUTF**, do not require efficacy and clinical studies, beyond what the supplier will have to provide for Good Manufacturing Practice (GMP) audit and product documentation to demonstrate compliance to the specification (e.g., stability studies, processing flow chart, test reports, etc).
- The consideration of clinical trials in animal models is an option but may not be practical in this context and are expensive.

The group, however, highlighted the need to define the domains of acceptability that should be reported. The group also proposed that alternative formulations that comply with the Codex RUTF guideline and the 2007 United Nations Joint Statement, the **WHO guidelines** and **Codex guideline for RUTF** need to provide evidence of the effect of changing the formulation on important factors such as antinutrient levels and micronutrient bioavailability. If no significant deviations are reported, the new formulations can be tested in a well-designed acceptability study to assess consumption over several weeks prior to introduction and scaling-up in programmes.

There is also a need for surveillance post use of these products such as monitoring for adverse events and monitoring efficacy outcomes from small pilots of these products in routine programmes.

Key message: Participants couldn't reach a consensus on when acceptability trials alone are adequate for new RUTF formulations (one group proposed that acceptability trials would be adequate for new RUTF formulations that follow the WHO and Codex guidelines, while the other group proposed that efficacy trials should be required for all new RUTF formulations). There were differing opinions between the two groups regarding the concept of an acceptability trial. Some group members referred to a taste trial used in sensory tests for food products as a reference to define acceptability trials. Others defined an acceptability trial as one which measures compliance of the consumption of RUTF as per the prescribed treatment protocol and therefore had a conceptual understanding of acceptability trials being of more robust design for longer duration than a food sensory trial.

Both groups agreed that the domains of acceptability should be defined, and an assessment of antinutrient risks need to be included as part of the trial design.

b. For new RUTF formulations that *do not follow* the specification in the technical annex of the 2007 United Nations Joint Statement: what are the best practices for generating evidence relating to efficacy, acceptability, resource use, and other domains?

The consensus in both groups was that, for all new formulations that do not follow the 2007 United Nations joint Statement, efficacy trials should be conducted, reflecting what was also agreed in previous meetings (e.g., the 2019 UNICEF expert meeting).[1] The need for consensus on the primary outcomes for efficacy trials was again emphasized.

[1] Fleet, Alison (ed.), *Expert meeting on ready-to-use therapeutic foods (RUTF), UNICEF, Supply Division, Report 1, 2–3 September 2019* United Nations Children's Fund, 2019, < **www.unicef.org/supply/documents/report-expert-meeting-ready-use-therapeutic-foods-rutf**>.

5. Conclusions

- RUTF product is an important, but not the major, cost in the treatment of children with severe wasting and/or nutritional oedema. Currently, it is difficult to estimate total programme costs, therefore the impact that new RUTF formulations can have on them is uncertain. However, to improve the availability of RUTF for treating children with severe wasting and/or nutritional oedema, the development and testing of new and alternative formulations should be encouraged.
- For the alternative RUTF formulations to be included in WHO guidelines, more evidence on efficacy, cost-effectiveness, acceptability, and feasibility needs to be generated. There is a need for consensus regarding the type and level of evidence that should be considered adequate to allow the alternative RUTF formulations to be used in programmes. For example, when designing efficacy trials there is a need for consensus on what should be considered primary outcomes for effectiveness (e.g., weight gain versus recovery rate). Similarly, when designing acceptability trials, there is a need for uniformity on how acceptability will be assessed (e.g., minimum duration of follow-up). These discussions are ongoing between UNICEF and WHO.
- It is required, as a minimum, that acceptability trials should be conducted on any new RUTF formulas. To ensure that the acceptability trials are conducted with the highest quality standards, expert advice from experienced researchers and programme managers is required in their design and implementation.
- Introduction of new RUTF formulation in programmes should include adequate monitoring to track any deviations from expected programme outcomes or longer-term adverse effects. This will facilitate data-collection for any unintended consequences and inform decisions for more efficient scale-up in similar contexts.

6. Next steps

- WHO is in the process of releasing a summary document that explains the key issues discussed by the guideline development group when formulating the recommendation for the WHO guideline on the protein content of RUTF. This summary will highlight the key gaps in the evidence presented, which led to WHO not changing the guidance in the 2007 United Nations Joint Statement that at least half of the protein in RUTF should come from dairy.
- An inter-agency working group is compiling a road map to develop the implementation guidance on the Codex guidelines for RUTF. This guidance will support stakeholders when developing, producing, rolling out, and monitoring different RUTF formulations to ensure that Codex international standards are adhered to.
- In parallel, a sub-working group will be formed under the Technical Advisory Group on wasting and/or nutritional oedema to address the question of whether new RUTF formulations that follow the Codex RUTF guidelines and WHO recommendations require efficacy and acceptability trials or acceptability trials alone. This sub-working group will also define the primary outcomes for effectiveness trials on new formulations of RUTF as part of the guidance document on research priorities. This sub-working group will also bring together a balanced mix of researchers, food regulators, and programme implementers to provide clear guidance on this topic.

Annexes

1. Meeting agenda

Day 1, Meeting objectives:
To discuss barriers and solutions to improve the availability and cost of RUTF

DAY 1 ■ 9 November 2021			
AGENDA			
Facilitator: Odile Caron			
1.	**OPENING**	Francesco Branca (WHO) and Victor Aguayo (UNICEF)	15:00–15:10
	Introduction Declaration of Conflict of Interest	Saul Guerrero Oteyza (UNICEF) and Zita Weise-Prinze (WHO)	15:10–15:30
2.	**SETTING THE SCENE: WASTING TREATMENT**		
	Cost of programming: the big picture	Lani Trenouth (UNICEF)	15:30–15:50
3.	**RUTF MARKET**		
	RUTF market influences and UNICEF market approach	Jan Debyser (UNICEF) and Philipp Kalpaxis (UNICEF)	15:50–16:10
4.	**RUTF: THE PRODUCT DETAILS**		
	Ingredients in RUTF and their associated costs	Alison Fleet (UNICEF) and Liang Zhao (UNICEF)	16:10–16:30
	Discussion and Q&A		16:30–16:40
	Break		**16:40–16:50**
	UNICEF Quality standards: Quality Assurance of RUTF	Peter Svarrer Jakobsen (UNICEF)	16:50–17:00
4.	**RUTF: THE PRODUCT DETAILS Continued….**		
	Next generation RUTF: categories of products	Alison Fleet (UNICEF)	17:00–17:15
	Indicative costs of alternative RUTF	Jan Debyser (UNICEF)	
5.	**PANEL DISCUSSION: Supplier Q & A**		
	Challenges and Opportunities with RUTF supply Supplier panel: *Compact, Insta, Nutriset*	*(Facilitator: Monica Rios)* Dhiren Chandaria (Insta Foods Kenya) Andrés Escalante, GC Rieber Compact Adeline Lescanne Gautier: Nutriset / Plumpyfield Network	17:15–17:55
6.	**Closing remarks**	*Saul Guerrero Oteyza*	17:55–18:00

Day 2, Meeting objectives:
Understand the WHO guideline process and discuss good practices for research on RUTF

DAY 2 ■ 10 November 2021			
AGENDA			
Facilitator: Ken Maleta			
1.	**RUTF composition**		
	Codex guideline for RUTF	Nolene Naiker (Department of Health, South Africa)	15:00–15:15
	Micronutrient levels in RUTF: Iron and essential fatty acids (EFAs)	Jaden Bendabenda (WHO)	15:15–15:25
	Impact of new formulations on micronutrient bioavailability	Maria Nieves Garcia Castel (WHO)	15:25–15.35
	Antinutrients in RUTF	Monica Rios (Supply Division, UNICEF)	15:35–15:40
	Questions and answers		15.40–15.50
2.	**Scientific evidence needed for new formulas of RUTF**		
	Defining WHO process for assessing evidence for global guidelines	Jaden Bendabenda (WHO)	15:50–16:05
	Summary of the Technical Expert Meeting on RUTF, 2019, Copenhagen report	Alison Fleet (UNICEF)	16:05–16:15
	Break		**16.15–16.25**
3.	**Best practice in trial design for new formulas of RUTF**		
	Trial designs for new formulas: • acceptability trials • efficacy trials	Group discussions (break-out sessions) (*Facilitators: Andrew Beckingham and Iris Bollemeijer*)	16:25–17:30
	Feedback from the group discussion		**17:30–17:55**
	CLOSING DAY 2	Francesco Branca (WHO) and Victor Aguayo (UNICEF)	17:55–18:00

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