Application for inclusion of Ready-to-Use Therapeutic Food (RUTF) on the WHO Model List of Essential Medicines (EML) and Model List of Essential Medicines for Children (EMLc)

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2. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

[For inclusions of new medicines or new indications for currently listed medicines, briefly describe the proposal in terms of clinical indication(s), target population(s) and role in therapy for the requested medicine(s).]

This submission proposes the inclusion of Ready to Use Therapeutic Food (RUTF) in the EML and EMLc for the treatment of severe acute malnutrition (SAM) in children older than 6 months. This proposal is being made to support the procurement and increase access to RUTF by national authorities in countries where SAM is prevalent.

Severe acute malnutrition is a condition which affects approximately 13.6 million children on an annual basis(1). SAM is associated with altered protein, glucose, and lipid metabolism. Metabolic dysregulations such as hypoglycaemia, impaired gluconeogenesis, disrupted amino acid or lipid metabolism are responsible for the different clinical manifestations of SAM and lead to the children suffering from it to be more susceptible to illness with a considerable increased risk of mortality.

Recovery from SAM requires high energy intake accompanied by high-quality protein and micronutrients. RUTF effectively balances the need to correct micronutrient and macronutrient deficiencies. RUTF supports the tissue synthesis required for catch-up growth.

Outpatient treatment for uncomplicated SAM (i.e. SAM without medical complications not needing inpatient admission) using RUTF is well established with over 5 million children admitted for treatment globally in 2021(2) using nutrition programmes with outpatient and inpatient care. (3).

More than 80% of RUTF used for the treatment of SAM is procured by UNICEF (4). To ensure sustainability and availability of this child survival intervention within national health systems, national authorities must engage in the procurement of RUTF. The presence of RUTF on the international EML will facilitate its' adoption at national level and increase the potential for national health authorities to procure RUTF as part of national health system planning,budgeting and integration into the health supply chains. (5)

3. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

[Applicants are encouraged to consult with relevant WHO technical departments as part of the submission preparation process. For submissions made following consultation with and support from the relevant WHO technical department, the name of the technical department and focal point(s) consulted should be included]

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4. OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

[The submission should indicate any other organization(s) that have been consulted in relation to the submission and/or support the submission. The affiliation between the applicant and the organization(s) should be specified. Letters of support from such organizations should be included in an Annex to the submission.]

Whilst the current submission has not involved consultations with partners, the previous application submitted in 2017 by Action Against Hunger included consultations with the following organisations:

Nutriset - Valid International - Médecins Sans Frontières (MSF) - Helen Keller international (HKI) - Baby Milk Action, a member of International Baby Food Action Network (IBFAN) - Society for International Development (SID)

National authorities and international stakeholders have also been consulted for their views and reports of these findings were also submitted in previous applications (6,7).

5. KEY INFORMATION FOR THE PROPOSED MEDICINE(S)

[International non-proprietary name (INN) of the proposed medicine(s)
Medicine(s) must be described using International Non-proprietary Names (INN) throughout the submission. INNs facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognised.
➢ A searchable database of INNs is available here.]

International non-proprietary name (INN) of the proposed medicine(s)
The product's generic name is Ready-To-Use Therapeutic Food (RUTF) developed for the treatment of SAM. The composition of this product is determined by the UN joint statement (3) and CODEX guidance (8). There is no explicit INN for the product itself, however the following active molecules with INNs are listed below:

Retinol, Thiamine, Riboflavin, Niacin, Pantothenic acid, Pyridoxine, Biotin, Folic acid, Cyanocobalamin, Ascorbic acid, Cholecalciferol, Tocopherol, Phytonadione, Sodium, Potassium, Calcium, Phosphorous, Magnesium, Iron, Zinc, Copper, Selenium, Iodine.

[Anatomical therapeutic chemical (ATC) code of the proposed medicine(s)
The Anatomical Therapeutic Chemical (ATC) system classifies medicines according to the anatomical organ or system upon which they act and by therapeutic, pharmacological and chemical subgroups. A single medicine may have more than one ATC code, depending on the indications for use.
➢ A searchable version of the complete ATC index is available here.]

Anatomical therapeutic chemical (ATC) code of the proposed medicine(s)
There is no ATC code for the product described. RUTF is intended to cover the special nutrient needs (macronutrient and micronutrients) of children with SAM to promote anthropometric recovery.

[Dosage form(s) and strength(s) of the proposed medicine(s)
The submission must identify the specific dose forms(s) and strength(s) of the medicine(s) for inclusion or deletion.
If the proposal relates to medicines for inclusion on the EMLc, the submission must address availability of suitable, age-appropriate dosage forms and strengths for administration to infants and children up to 12 years of age.

Dosage form(s) and strength(s) of the proposed medicine(s)
The recommended dosage is 150 to 220 kcal/kg body weight/ day of RUTF for children aged between 6-59 months suffering from severe acute malnutrition to be consumed until anthropometric recovery. The RUTF can be in a biscuit or paste form.

[Indication(s)
The indication(s) for which the medicine(s) is proposed for inclusion or deletion must be clearly specified. When available, the appropriate code for the proposed indication using the International Classification of Diseases, 11th Revision (ICD-11) must be included.
➢ A searchable database of ICD-11 codes is available here.]

Indications
Code: 5B52&XS25
5B52 Acute malnutrition in infants, children or adolescents. XS25 Severe acute malnutrition

To be given to children 6-59 months with severe acute malnutrition who are either: 1) in an inpatient centre and clinically stable (cardiovascularly stable, neurologically stable/not deteriorating, has adequate protective airway reflexes and a normal abdominal examination) to transition from therapeutic milks to RUTF or 2) in an outpatient centre with adequate appetite and no medical complications needing inpatient admission to be able to consume the RUTF at home. The RUTF should be given until anthropometric and clinical recovery.

6. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP.

[The submission must indicate if the proposal relates to listing of an individual medicine or listing for one medicine as the representative of one or more therapeutic alternatives (“square box” listing).]

The listing is requested as an individual medicine.

7. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

[Submissions for inclusion of new medicine(s) and/or indication(s) must include information and evidence supporting the public health relevance of the proposed medicine(s), including:
• Epidemiological information on disease burden
• Target population(s)
• Alternative medicines currently included on the Model Lists for the proposed indication(s)]

Severe acute malnutrition in children aged 6-59 months is defined anthropometrically using any one or combination of the following criteria: a mid-upper arm circumference (MUAC) <115 mm or a weight-for-height <–3 Z-scores of the WHO growth standards, or bilateral nutritional oedema(3). This target population are identified through passive and active screening at health facilities and at community level and this is integrated into national health systems using the CMAM model. Children detected as SAM presenting specific and severe medical complications or with complete anorexia are referred for inpatient care treatment while children detected as having SAM but not needing inpatient treatment and with a preserved appetite are admitted into outpatient care using RUTF treatment alongside the appropriate medical treatment and follow-up.

Rates of SAM in children have remained persistently high and progress towards the SDG of reducing child wasting (which includes children with both MAM and SAM by weight-for-height Z scores) to <5% by 2025 has been limited (2). SAM affects approximately 13.6 million children under the age of five on an annual basis in low and lower-middle income countries (1). Some of the highest prevalence rates of the condition are located in countries in east and west Africa,

however, the majority of children suffering from SAM live in Asia(1). More specifically, over half of all children suffering from SAM live in southern Asian countries (1). Whilst SAM has typically been linked to humanitarian contexts, 3 out of 4 children suffering from SAM do not live in contexts affected by humanitarian crises (2) demonstrating that this condition is a widespread public health concern.

In the current context of climate change, creating persistent drought, elevated food prices and the impact of COVID-19, the rates of SAM are rising in many countries. Since the beginning of 2022, 260,000 additional children are expected to suffer from SAM in 15 of the most high burden countries, an equivalent to one child every minute deteriorating to have SAM (9). In some countries, Afghanistan for example, rates of acute malnutrition have doubled in the last five years (10). This worsening of the situation calls for immediate and sustained efforts to increase access to care for these children with a vital aspect being increasing the availability of RUTF particularly in high burden countries (11).

There are no other items listed on the WHO model EML for the nutritional rehabilitation of severe acute malnutrition. Antibiotics and antihelmintics, which are prescribed in conjunction with RUTF appear on the EML.

8. TREATMENT DETAILS

[Dosage regimen and duration of treatment :For inclusion of new medicines or new indications, the submission should describe the proposed therapeutic dosage regimen and duration of treatment for each medicine and indication. This should be informed by experimental, regulatory, and real-world data.
[Requirements to ensure appropriate use of the medicine(s): Consideration must be given to any additional requirements associated with appropriate use of the medicine, and avoidance of inappropriate use of the medicine(s); such as patient age and/or weight restrictions, diagnostic tests, specialized treatment facilities, administration requirements, monitoring requirements and skill levels of health care providers.]

Therapeutic dosage regimen and duration of treatment:

According the existing guidance(3), children suffering from SAM should receive 150 to 220 kcal/ kg/ day of RUTF until anthropometric recovery. This dosage range is often translated into quick dosing tables (by Ministries of Health or other implementing organisations) to facilitate the prescription for health care workers with low levels of clinical training..

Children can be discharged from treatment when the following anthropometric criteria are met:

- Weight-for-height/length (WHZ) ≥–2 Z-score (for children admitted by WHZ) and no oedema for at least 2 weeks, or
- Mid-upper-arm circumference (MUAC) ≥125 mm (for children admitted by MUAC) and no oedema for at least 2 weeks.

There is no specific duration of treatment given that recovery is dependent on the aforementioned anthropometric criteria. If a child is not responding to nutritional treatment or developing medical complications, they may be referred to in-patient care at the nearest available facility(12).

Requirements to ensure appropriate use of the medicine(s):

In line with national protocols for the treatment of severe acute malnutrition, only trained health staff (facility or community based) can admit children for the treatment of SAM. Admissions are usually based on the following anthropometric criteria:

- weight-for-height ≤–3 Z-score, or
- mid-upper-arm circumference <115 mm, or
- presence of bilateral nutritional oedema;

To detect SAM, height boards, scales and MUAC tapes are necessary. Health workers and community health workers administering treatment are trained using WHO guidelines and national protocols on anthropometry.

Prior to admitting a child for treatment using RUTF, health workers must conduct a clinical examination to assess for any medical complications needing inpatient admission and conduct an appetite test to ensure the child can consume RUTF at home. If complications are identified or the child fails the appetite test, the child should be admitted for inpatient care at the nearest facility(13).

On admission, health staff are required to fill patient data in official registers. In addition to anthropometry, the age, sex, date of admission and quantity of RUTF administered are recorded. This data is usually escalated to national level through institutional information systems (e.g. DHIS) for national health surveillance and planning purposes.

[Recommendations in existing WHO guidelines: Is the proposed medicine(s) recommended for use in current WHO guidelines? If yes, please provide summary details, including the strength of the recommendation and certainty of the evidence.]

RUTF is currently recommended for use in the following guidelines:

- WHO. Community-based management of severe acute malnutrition, A Joint Statement, World Health Organization, World Food Programme, United Nations System Standing Committee on Nutrition and United Nations Children's Fund, 2007 (3)
- WHO. Guideline: Updates on the management of severe acute malnutrition in infants and children. 2013 (13)
- WHO guideline on the dairy protein content in ready-to-use therapeutic foods for treatment of uncomplicated severe acute malnutrition. Geneva: World Health Organization; 2021.

Recommendations in other current clinical guidelines : Is the proposed medicine(s) recommended for use in other current clinical guidelines? If yes, please provide details of the recommendation(s) and full reference to the guideline(s) concerned.

A recent mapping exercise conducted by UNICEF has identified 71 countries with national clinical guidelines on the management of SAM which includes treatment with RUTF(14). 10 additional countries have draft or interim guidance on the management of SAM using RUTF (14).

9. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

[Submissions must include a summary of the available clinical evidence to support the comparative effectiveness of the proposed medicine(s) for the proposed indication(s).

Wherever possible, systematic reviews and meta-analyses should be presented. These may be from the published literature or conducted de novo by the applicant(s). When systematic reviews and meta-analyses are conducted by applicants for the purpose of the submission, this should be clearly indicated.

Evidence from individual randomized controlled trials can be presented showing patients characteristics, baseline risk for the main relevant outcomes in the standard treatment arm, absolute differences and measures of association.

Adequate consideration must be given to the quality of the studies (or risk of bias of individual study) together with comments on applicability/generalizability of the trial data (population, interventions, outcomes chosen), and on inconsistency among studies which may reduce the quality of the evidence.

Summaries of evidence from key trials using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tables should be included in the submission to support the comparative effectiveness and comparative safety of the proposed medicine(s).

Systematic literature search
The submission must include information on the identification of clinical evidence using a systematic literature search (search strategy, search terms, inclusion and exclusion criteria, search results).

Summary of available evidence for comparative effectiveness
The submission should summarize the available data including an appraisal of quality of the evidence, outcome measures and results. Include a summary of trial-based estimates of comparative effectiveness (including the number of participants and events; and measures of relative and absolute treatment effects). Preference must be given to comparisons with medicines already listed in the

Model Lists or recognized standard(s) of care.
Assessment of applicability of the available evidence across diverse populations and settings
Evidence from a variety of clinical settings, including settings with different income levels and resources should be included, whenever available.

Submissions must evaluate evidence for both adults and children (when applicable to the proposed medicine), and for different patient populations (e.g. patients of different genders and ethnicities, pregnant and breastfeeding patients, elderly patients etc.) Where such evidence is not available, this should be clearly stated and the submission should present an assessment of the applicability of the available evidence to these different populations and settings.]

The use of RUTF for the outpatient treatment of SAM in children 6-59 months of age is well established and has been a recommended treatment approach for over fifteen years. The 2007 Joint Statement issued by the WHO, WFP, UNICEF and the UNSSC on Nutrition highlighted the importance of community-based treatment of SAM with RUTF and recommended this approach for uncomplicated cases of SAM. The Joint Statement went further to advocate the importance of national protocols and provision of RUTF for the management of SAM (3). The 2013 WHO guideline updates for the management of SAM recommend outpatient treatment for children who have passed an appetite test and are clinically well. Despite the low quality of evidence identified, these guidelines include ***a strong recommendation for the use of RUTF for outpatient treatment*** (13).

These recommendations are based on a substantial body of observational and programmatic data but limited impact studies of high quality. Two systematic reviews on the use of RUTF were published in 2013. (18,19) Both reviews used GRADE criteria to assess the available evidence base.

The 2013 Cochrane Review included three quasi-randomized trials comparing RUTF with a standard flour porridge diet for the treatment of SAM. The meta-analysis found that RUTF improved recovery slightly (RR 1.32; 95% confidence interval 1.16 to 1.50) but the evidence was too limited to draw definitive conclusions on relapse, mortality or weight gain (18). This review was updated and republished in 2019 with an additional 11 studies being included, bringing the total amount of studies to 15. The revised review concludes that RUTF likely contributed to improved recovery and weight gain, however the effects on relapse and mortality remain unknown (18). Different formulations of RUTF were compared with increased benefits of a particular formulation over another (18).

A systematic review, meta-analysis and Delphi process on the treatment of severe and moderate acute malnutrition published in 2013 compares children who received RUTF with those who received standard care (in-patient treatment with therapeutic milks followed by provision of corn soy blend (CSB) food for feeding at home). The evidence was also noted as low quality and limited (largely the same as studies included in the Cochrane Review). However, the review and meta-analysis found that children given RUTF were 51% more likely to achieve nutritional recovery (WHZ ≥ -2) than the standard care group (RR: 1.51; 95% CI 1.04 – 2.20). Weight gain in the RUTF group was also higher, this was statistically significant but small (MD: 1.27; 95% CI 0.16 – 2.38). There were no significant differences in mortality between the two groups (19).

Due to the limited number of high-quality comparative trials evaluating community-based treatment using RUTF, Lenters et al complemented the systematic review and meta-analysis with a Delphi process to gather and synthesize expert opinion on the plausible impact estimates of the intervention. For community-based treatment of uncomplicated SAM using RUTF, the Delphi process estimated case fatality rate to be at 4% (range: 2-7%), and a recovery rate of 80% (range: 50-93%). Overall, the review argues that the management of uncomplicated SAM in children 6-59 months of age using RUTF is backed by a wealth of observational and programmatic data, despite the limited number of impact studies (19).

Since these reviews were published in 2013, a handful of additional studies have been published documenting the acceptability of RUTF formulation and program evaluation. However, only one additional clinical trial was found. The single additional clinical trial identified was a cluster randomized trial in India of 26 children with SAM. The study found that children who received RUTF in addition to standard supplementary nutrition (roughly 500 kcal of energy and 12-15g protein provided at Anganwadi centers under the Integrated Child Development Scheme) were 10 times more likely to recover (odds ratio 10.28; 95% CI1.02-104.95) (20).

A study was conducted to assess the effects of RUTF on recovery, relapse, mortality and rate of weight gain, a random-effects meta-analysis was carried out for selected randomised controlled trials (RCTs) and quasi-RCTs, where children aged between six months and five years with SAM were, during the rehabilitation phase, treated with RUTF compared to an alternative dietary approach. It was found that RUTF improves recovery (risk ratio (RR) 1.33; 95% confidence interval (CI) 1.16 to 1.54. The findings suggest that RUTF is effective compared with other evidence (17).

As highlighted in the Lenters et al review, there are very few impact and effectiveness trials for RUTF published. This reflects the broader community's acceptance of strong programmatic data documenting high recovery rates and, just as importantly, higher coverage rates than are possible through in-patient treatment of severe acute malnutrition. Current research is focused on developing equally effective but cheaper formulas of RUTF that can be produced locally and improving program quality to increase coverage and quality.

10. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY

Submissions must include a summary of the available clinical evidence describing the safety of the proposed medicine(s) for the proposed indication(s).
Submissions should include the following:
• Estimates of total patient exposure to date
• Information on the identification of clinical evidence using a systematic literature search (search strategy, search terms, inclusion and exclusion criteria, search results).
• A summary of the available clinical evidence, including appraisal of quality and analysis of findings
• Descriptions of adverse effects of the proposed medicine(s) and estimates of their frequency and grading of severity
• A summary of comparative safety versus relevant comparators
• Consideration of the potential for and consequences of inappropriate use or use outside the proposed indication
• Information on any variation in safety that may relate to health systems or patient factors.
• Information on any warning or safety issues identified by regulatory authorities (e.g., black box warning, drug safety alerts etc).

RUTF are high-energy, fortified, ready-to-eat foods for the treatment of SAM in children 6-59 months of age. The evidence presented here on both effectiveness and harms is focused on the most commonly used formula, which is peanut-based with added milk powder among other ingredients. Unlike F-100, all RUTF formulas are not water-based, limiting bacteria growth. They can be transported and stored without refrigeration and in areas where hygiene conditions are sub-optimal (3).

Peanuts, chickpeas and soybeans— the main raw commodities used in lipid-based Ready to use Foods (RUF) formulations—contain a wide range of naturally occurring microorganisms, some capable of causing human diseases. Therefore, even low-moisture foods with sufficiently low water activity to prevent the growth of bacteria can be vehicles of pathogens. Children with acute malnutrition may be more susceptible to foodborne illnesses because changes caused by malnutrition may impact on their ability to defend against pathogens. RUF include atrophy of lymphoid tissues (e.g. tonsils, thymus and gut-associated lymphoid tissue); decreased antibody production, including of the antibody type (IgA) that is secreted into the digestive system; decreased cell-mediated immunity; poorly functioning complement and cytokine systems; decreased production of gastric acid (the first major barrier to ingested foodborne pathogens); decreased intestinal motility and barrier function; decreased production of intestinal mucus; and hepatic dysfunction, including decreased bile production.(27)
For peanut based RUTFs, the largest safety concern for the product is contamination by the bacterial pathogen Salmonella. Salmonellosis can pose a health risk by very low doses in some foods (e.g. foods with high lipid content) and its link to foodborne disease outbreaks is well established. (27)
Aflatoxin present in peanuts and milk must also be controlled as chronic consumption of high levels is associated with chronic toxicity. Exposure in early life can impact on child growth, development, immune and hepatic systems. (28)
There is a theoretical concern of vitamin toxicity for vitamins A, D and E as these are present in doses higher than the recommended daily intakes. The dosage regime suggested can bring deficient children to a replete status, thus the high doses of nutrients is required by the target population. However, there is a risk for toxicity of fat-soluble nutrients vitamin A, D and E if RUTF is consumed by an unintended consumer. .
The recently finalised text for the Codex Guideline for Ready to Use Therapeutic Food includes appropriate food safety guidance for microbiological, chemical and physical hazards associated with RUTF and its production. (26)

The 2013 Cochrane Review included a review of the safety of RUTF, including a comparison of the mortality, frequency diarrhoea, and adverse outcomes between RUTF and the standard flour porridge diet. There was no difference in mortality between the children who received RUTF and those who received standard diets (RR 0.97; 95% CI 0.46 – 2.05; n = 599). Similarly, there was no difference in the frequency of diarrhea (number of days of diarrhea in the first two weeks of treatment) between the children who received RUTF and those who received the standard diets (MD -0.6; 95% CI -1.30 to 0.10; n=352). In addition, the WHO guideline updates in 2013 stated that empirical data to suggest that RUTF either increases the incidence of diarrhea or worsens diarrhea among children with SAM (13). There were no further reports of adverse outcomes, including allergic reactions reported(19) .

11. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS

The submission should include a summary of available data on the price of the medicine(s) in different markets, the estimated budget impact to patients and health systems, and data from economic analyses (e.g. cost-effectiveness, cost-utility studies) of the proposed medicine(s) versus other pharmacological or therapeutic interventions.

Data from cost-effectiveness and cost-utility analyses performed at national level should be included where available to provide general information on whether the intervention provides good value for money compared to alternative treatments already listed. The setting, willingness-to-pay threshold and the perspective from which the analyses were conducted should be clearly indicated.
The submission should consider the overall financial impact to health systems of making the medicine available.

Information on any special pricing arrangements, where they exist, should be included.
To justify the potential inclusion of medicines that incur greater costs to patients and health systems, the submission should clearly demonstrate the advantages of the proposed medicine relative to any currently listed medicines in key dimensions such as benefits, harms, compliance, ease of use, as an alternative for patients with allergies or other contraindications to already listed medicines, or non-responders to already listed medicines, etc.

Cost and cost-effectiveness of Treatment using RUTF

The evidence on costs and cost-effectiveness of large-scale programs using RUTF for the outpatient treatment of SAM in children 6-59 months of age is limited but growing. A recent review, conducted by Action Against Hunger and Save the Children published in 2020, brought together all the existing literature on cost and cost-effectiveness for SAM treatment. In total, this review identified 21 different studies of which 20 studies report cost per child admitted and 11 report cost-effectiveness data (22). The details of these studies reporting on costs using RUTF are listed in the table below.

STUDY	COUNTRY	OTP/ CHW/ INPATIENT	COST/ CHILD ADMITTED FOR TREATMENT (US$)
Abdul Latif & Novignon, 2014	Ghana	OTP	$805
Ali et al., 2017	Nigeria	OTP	$131
		OTP	$117
Bachman, 2009	Zambia	OTP	$203
IRC, 2016	Yemen	OTP and inpatient	$797
	Yemen	OTP and inpatient	$358
	Mali	OTP and inpatient	$336
	Mali	OTP and inpatient	$329
	Niger	OTP and inpatient	$142
	Kenya	OTP and inpatient	$141
	Mali	OTP and inpatient	$120
	Kenya	OTP and inpatient	$119

Isanaka et al., 2016	Niger	OTP	$ 76
Lelijveld et al., 2018 and Bailey et al., 2020	Kenya, South Sudan	Standard protocol	$451
		Simplified protocol	$435
Puett et al., 2013	Bangladesh	CHW	$165
Rogers et al., 2018	Pakistan	OTP	$301
		CHW	$291
Rogers et al., 2019	Mali	CHW	$244
		OTP	$442
Sharma and Matafeni, 2017	Yemen	OTP and mobile clinics	$302
Tekeste et al., 2012	Ethiopia	OTP	$135
UNICEF, 2012a	Kenya	OTP	$94
UNICEF, 2012b	Pakistan	OTP	$145
UNICEF, 2012 c	Ethiopia	OTP	$110
UNICEF, 2012d	Nepal	OTP	$77
UNICEF, 2012e	Chad	OTP and inpatient	$196
Wilford et al., 2011	Malawi	OTP	$169

The studies span countries in Africa and South Asia and were conducted between 2009 – 2019. On average, according to these studies, SAM treatment costs $262 per child with a median cost of $196. Total costs for the treatment service per child admitted range from $76 in Niger to $805 in Ghana. These costs include RUTF procurement and transportation, as well as costs of delivery including infrastructure, health worker time, additional drugs delivered with the treatment package, community outreach and screening activities and others.

The wide range in cost per child reflects the varying methods contexts, scale, and models of implementation. For example, in the Ghana study, only 40 children were treated. Such low level of admissions where services are scaled can dramatically drive up the cost per child treated. (22) Another factor influencing the large variation in costs is linked to the methodology used and the sources of cost information included. Across studies there was a large variation in the costs included. (22)

While total cost of treatment can vary significantly, the absolute cost of RUTF is more consistent across programs. In the most recent Market Outlook published by UNICEF Supply Division, it is stated that one carton of RUTF (150 sachets) is sufficient to treat a child over 6-8 weeks. (4) UNICEF procure 75-80% of RUTF globally and have effectively driven down the cost per carton from $52 in 2006 to $41 in 2021.(11) In programs with larger total costs, RUTF accounts for a much smaller portion of the total cost (RUTF was 13% of the total cost of treatment in Ghana - $805) and vice versa (RUTF was 46% of the total cost of treatment in Nigeria - $106). This demonstrates that total treatment cost is largely driven, not by the cost of RUTF, but by the context, scale and quality of the program.

It is important to note that product price reductions achieved over the last 16 years risk being reversed due to the current global context which is seeing rises in prices of ingredients, packaging, energy and international freight, leaving the next 18-24 months with a very uncertain outlook. (11). In July 2022, UNICEF estimated that the price of one carton of RUTF increased by 16%. Immediate funding increases are needed and efforts to widen the availability of RUTF accelerated in order to respond to this increase in price and the escalating needs (11,25).

Cost-effectiveness of treatment with RUTF:
Whilst the evidence pertaining to cost-effectiveness of treatment of SAM is limited, treatment with RUTF using the community-based model is considered a highly cost-effective intervention. Six studies included in the review assess the cost per disability-adjusted life year (DALY) averted, demonstrated in the table below.

STUDY	COUNTRY	COST/ DALY AVERTED (US$)
Ali et al., 2017	Nigeria	$48
Bachman, 2009	Zambia	$53
Frankel et al. 2015	Nigeria	$30
Puett et al., 2013	Bangladesh	$26
Wilford et al., 2011	Malawi	$42

The cost per DALY averted ranges from $26 in Bangladesh to $ 53 in Zambia. Given that these estimates fall below the GDP per capita in the countries where implemented, the intervention is considered to be cost effective (22) These cost-effectiveness estimates demonstrate that the treatment of SAM is both cost-effective and comparable to the cost-effectiveness of other child survival interventions. However, it is important to note that these estimates are dependent upon several factors and subsequently have wide confidence intervals.

12. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS

The submission must provide a summary of the regulatory status of the medicine(s) proposed and including the indication(s) for which the medicine(s) has regulatory approval.

Off-label indication(s) may be considered where off-label use is supported by evidence.

Regulatory status of the proposed medicine(s)
Submissions should include details of the regulatory status of the medicine(s) from national regulatory authorities.
➢ Information regarding Stringent Regulatory Authorities (SRAs) and/or WHO-Listed Authorities (WLAs), including an interim list of National Regulatory Authorities, is available here.

To establish the current regulatory status of RUTF within national regulatory bodies, UNICEF conducted an internal survey targeting all countries where SAM services are available. Details of the methodology can be found in the annex report submitted in conjunction with this application.

Currently there is no appropriate category on the WHO EML within which RUTF can fit. Following this application, UNICEF and WHO NFS department will submit a proposal to the WHO EML Secretariat to develop an appropriate category for therapeutic foods recommended by WHO.

Status of inclusion of RUTF in national EML

As of November 2021, 25 countries (36%) with programmes to treat SAM with RUTF had included RUTF in their country's national EML (*Table 1*). The percentage of countries with RUTF in the national EML was considerably higher in the Africa Region (63%) than elsewhere: only 18% countries in the Region of the Americas and one in ten of the countries in West Pacific had included RUTF in the national EML, and none in the Eastern Mediterranean Region, Europe Region or Southeast Asia Region, but some countries are in the process to request for its inclusion. The data by country are provided in Annex 2.

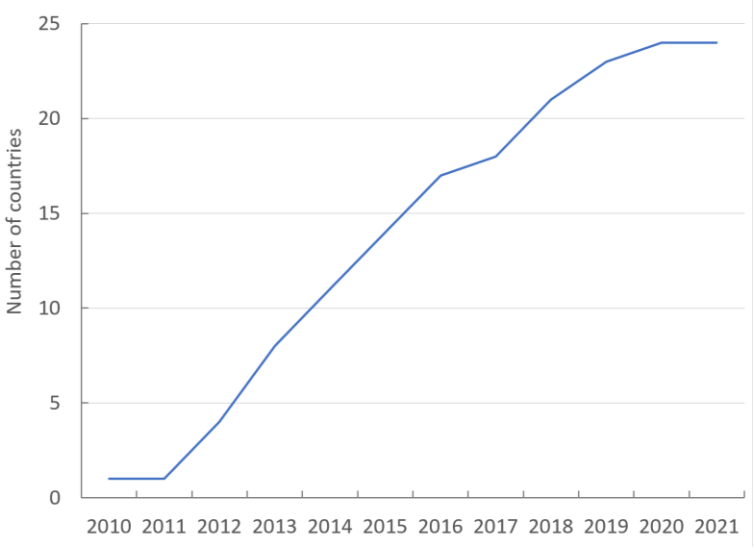
Table 1: Number and percentage of countries that have included RUTF in the national EML by WHO region

	Number of countries	Countries with RUTF in national EML	
		Number	Percentage (%)

Africa Region	35	22	74
Region of the Americas	11	2	18
Eastern Mediterranean Region	7	0	0
Europe Region	2	0	0
South-East Asia Region	4	0	0
West Pacific Region	10	1	10
All regions	69	25	36

Figure 1 shows that the cumulative number of countries with RUTF in the national EML increased steadily between 2010 and 2019 but has since plateaued.

Figure 1: Cumulative number of countries with RUTF in the national EML by year (24 countries)



Only two countries reported that a decision had been taken to not include RUTF in the national EML, citing its absence on the model EML meant that it was not considered an essential product at national level. Eighteen countries reported that they were in the process of deciding whether to include RUTF in the national EML and 19 countries had not started a process.

Classification of RUTF and regulatory agency

Most of the 25 countries with RUTF in the national EML have classified RUTF as a medicine (11 countries) or food for special medical purposes (7 countries) (*Table 3*) and have assigned a medicines regulatory authority (18 countries) or a combined food and drug regulatory authority (2 countries) to regulate RUTF (*Table 4*).

Table 3: RUTF classification in counties with RUTF in the national EML (n=25 countries)

	Number	Percentage
Medicine	11	44
Food for special medical purposes	7	28
Other	7	28

Table 4: Agency that regulates RUTF in countries with RUTF in the national EML (n=25 countries)

	Number	Percentage

Medicines regulatory authority	18	72
Combined food and drug regulatory authority	2	8
Standards agency	1	4
Other	4	16

Regulating composition and manufacturing: The implications of the new CODEX Guidance on RUTF

In 2022 the CODEX Guideline for Ready to Use Therapeutic Foods (RUTF) text has been finalised presenting the first international reference document detailing the composition and manufacturing standards for RUTF.

The publication of these guidelines provides a series of opportunities for the availability and sustainability of treatment services for children with SAM. Firstly, these guidelines provide an official international reference for use by national governments. The presence of an internationally approved regulatory framework is a key enabling factor in the integration of treatment services for SAM at national level. Many elements of the service delivery are already integrated into national health systems to varying degrees depending on the country. Over the last decade, UNICEF has been focussing efforts to integrate RUTF into national supply chains and secure domestic funding for this life-saving product. Modest gains have been made by governments in high burden countries, though UNICEF continues to procure the majority of RUTF (75-80%) for the treatment of SAM. The availability of recognised international guidelines is expected to support the integration process by providing national governments with a regulatory framework which can be applied at country level to ensure quality and standards. These independent guidelines will be able to orient governments in the procurement process and will also be an essential tool to assist in building regulatory capacity within national governments to establish their own regulatory framework for RUTF.

Secondly, this guideline clarifies the regulatory status of RUTF as a Food for Special Medical Purposes (FSMP). One of the key concerns in listing RUTF on the EML raised in stakeholder consultations in 2018 was that this listing might lead to the application of pharmaceutical standards to the manufacturing process. The CODEX guidelines have effectively determined that RUTF sit within the regulatory frameworks of food production, with a focus on the fact that this product is for specific medical purposes. The approach of classifying RUTF as an FSMP will assist member states in clarifying that the products are specially processed or formulated, highlighting that this product is only for use in the treatment of SAM, not for general consumption.

Thirdly, this guidance provides a clear framework for producers with an associated set of quality standards. As highlighted, to date, UNICEF and partners have determined specific guidance in the absence of a regulatory framework. Whilst this guidance has been enabling for some suppliers, the market may now become more open for new suppliers given this international guidance. The availability of these guidelines could this be helpful for suppliers and it could also open a pathway for innovation and local acceptability with generic compositional specification with guidance on quality.

Finally, and importantly, these guidelines can be used to facilitate trade disputes and importation requirements. The guidelines are intended for use as an instrument designed to avoid or reduce difficulties which may be created by diverging legal, administrative and technical approaches to RUTF and by varying definitions and nutrient compositions of RUTF.

Further details are available in the Annex reports submitting alongside this application.

Market availability of the proposed medicine(s)
The submission must provide information regarding the market availability of the medicine(s) in a variety of settings, including patent status and, where appropriate, any existing or planned licencing agreements with generic manufacturers and/or the Medicines Patent Pool.

Reference to existing or planned inclusion of the proposed medicine(s) on the WHO List of Prequalified Finished Pharmaceutical Products, should be included, where appropriate.
Pharmacopoieal standards The submission must indicate the availability of pharmacopoieal standards for the medicine(s) proposed in the British, European, International and United States Pharmacopoieas. 15

To date the product is not included in the International, British, United States or European Pharmacopoeia.

13. REFERENCES

The submission must be clearly referenced with in-text citations using Vancouver style.
Electronic reference library files must be exportable from the Word version of the submission document or provided separately.

1. UNICEF, WHO WB. Levels and trends in child malnutrition: Joint Child Malnutrition Estimates. Key findings of the 2021 edition. World Heal Organ [Internet]. 2021;1–32. Available from: https://www.who.int/publications/i/item/9789240025257
2. UNICEF. No time to waste: UNICEF's approach for the prevention, early detection, and treatment of wasting in early childhood. 2021.
3. World Health Organization, World Food Programme, UNICEF. Community Based Management of Severe Acute Malnutrition: A Joint Statement. 2007.
4. UNICEF Supply Division. Ready-to-Use Therapeutic Food: Market Outlook. 2021;(February):0–11. Available from: https://www.unicef.org/supply/media/421/file/Ready-to-use therapeutic food (RUTF) market outlook.pdf
5. du Châtelet A, Webb M, Israël A. Process and impact of integration of ready-to-use therapeutic foods in national essential medicines lists. In: WHO technical consultation: Nutrition-related health products and the World Health Organization Model List of Essential Medicines. 2019; Available from: https://www.who.int/docs/default-source/nutritionlibrary/publications/nutrition-related-health-products-and-the-world-health-organization-model-list-of-essential-medicines-practical-considerations-and-feasibility/lem-du-chatelet-et-al-2019.pdf?sfvrsn=46b0
6. Adams KP, Dewey KG. Stakeholder perceptions of adding ready-to-use therapeutic foods and other nutrition-related products to the World Health Organization Model List of Essential Medicines. 2019;68–87.
7. Dedios MC, Beltran-velazquez F. Expert assessments of the inclusion of ready-to-use therapeutic foods in the World Health Organization qualitative evaluation. 2019;45–67.
8. Codex Alimentarius Commission. PROPOSED DRAFT GUIDELINES FOR READY-TO-USE THERAPEUTIC FOODS. Jt FAO/WHO FOOD Stand Program CODEX Comm

Nutr FOODS Spec Diet USES [Internet]. 2017;23(4):1–10. Available from: https://www.proquest.com/scholarly-journals/discerns-special-education-teachers-about-access/docview/2477168620/se-2?accountid=17260%0Ahttp://lenketjener.uit.no/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&genre=article&sid=ProQ:ProQ%3Aed

9. UNICEF. Global hunger crisis pushing one child into severe malnutrition every minute in 15 crisis-hit countries. 2022. p. 1–8.

10. UNICEF. World a ‘ virtual tinderbox ’ for catastrophic levels of severe malnutrition in children. 2022. p. 1–8.

11. UNICEF Supply Division. Ready-to-Use Therapeutic Food Supply Alert - June 2022. 2022;(June).

12. Golden M, Grellety Y. Integrated Management of Acute Malnutrition: Protocol. 2011.

13. World Health Organization (WHO). Guideline: updates on the management of severe acute malnutrition in infants and children. 2013.

14. UNICEF. Mapping of National CMAM Protocols. 2022.

15. Sato W, Furuta C, Matsunaga K. Amino-acid-enriched cereals ready-to-use therapeutic foods (RUTF) are as effective as milk-based RUTF in recovering essential amino acid during the treatment of severe acute malnutrition in children: An individually randomized control trial in Malawi. PLoS One. 2018;13(8).

16. Shokry E, Sadiq K, Soofi S, Habib A, Bhutto N, Rizvi A, et al. Impact of Treatment with RUTF on Plasma Lipid Profiles of Severely Malnourished Pakistani Children. Nutrients. 2020;12(7).

17. Akomo P, Bahwere P, Murakami H, Banda C, Maganga E, Kathumba S, 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. 2019;19(1):1–15.

18. Schoonees A, Lombard MJ, Musekiwa A, Nel E, Volmink J. Ready-to-use therapeutic food (RUTF) for home-based nutritional rehabilitation of severe acute malnutrition in children from six months to five years of age. Cochrane Database Syst Rev. 2019;2019(5):3–6.

19. Lenters LM, Wazny K, Webb P, Ahmed T, Bhutta ZA. Treatment of severe and moderate acute malnutrition in low- and middle-income settings: A systematic review, meta-analysis and Delphi process. BMC Public Health. 2013;13(SUPPL.3).

20. Shewade HD, Patro BK, Bharti B, Soundappan K, Kaur A, Taneja N. Effectiveness of indigenous ready-to-use therapeutic food in community-based management of uncomplicated severe acute malnutrition: A randomized controlled trial from india. J Trop Pediatr. 2013;59(5):393–8.

21. Potani I, Spiegel-Feld C, Brixi G, Bendabenda J, Siegfried N, Bandsma RHJ, et al. Ready-to-Use Therapeutic Food (RUTF) Containing Low or No Dairy Compared to Standard RUTF for Children with Severe Acute Malnutrition: A Systematic Review and Meta-Analysis. Adv Nutr. 2021;12(5):1930–43.

22. Chui J, Donelly A, Cichon B, Mayberry A, Keanr E. The Cost-efficiency and Cost-effectiveness of the Management of Wasting in Children: A review of the evidence, approaches. 2020;

23. Bailey J, Opondo C, Lelijveld N, Marron B, Onyo P, Musyoki EN, et al. A simplified, combined protocol versus standard treatment for acute malnutrition in children 6–59 months (ComPAS trial): A cluster-randomized controlled non-inferiority trial in Kenya and South Sudan. PLoS Med. 2020;17(7).

24. Rogers E, Guerrero S, Kumar D, Soofi S, Fazal S, Martínez K, et al. Evaluation of the cost-effectiveness of the treatment of uncomplicated severe acute malnutrition by lady health workers as compared to an outpatient therapeutic feeding programme in Sindh Province, Pakistan 11 Medical and Health Sciences 1117 Public Healt. BMC Public Health. 2019;19(1):1–11.

25. UNICEF. Severe wasting An overlooked child survival emergency An overlooked child survival emergency. 2022.

26. Report of the Forty-second session of the Codex Committee on Nutrition and Foods for Special Dietary Uses Virtual 19-25 November and 1 December 2021. https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-720-42%252FFINAL%252520REPORT%252FREP22_NFSDUe.pdf

26. FAO/WHO [Food and Agriculture Organization of the United Nations/World Health Organization]. 2016. Microbial safety of lipid-based ready-to-use foods for management of moderate acute malnutrition and severe acute malnutrition. Microbiological Risk Assessment Series No. 28. Rome. 66pp

27. AmirIsmailaIqraNaeemaYun YunGongbMichael N.RoutledgecdSaeedAkhtaraMuhammadRiazaLeandra Naira ZambelliRamalhoeCarlos Augusto Fernandesde OliveirafZubairIsmail. Early life exposure to dietary aflatoxins, health impact and control perspectives: A review. Trends in Food Science & Technology Volume 112, June 2021, Pages 212-224