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Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age (Review)

Schoonees A, Lombard M, Musekiwa A, Nel E, Volmink J

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Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

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ABSTRACT

Background

Malnourished children have a higher risk of death and illness. Treating severe acute malnourished children in hospitals is not always desirable or practical in rural settings, and home treatment may be better. Home treatment can be food prepared by the carer, such as flour porridge, or commercially manufactured food such as ready-to-use therapeutic food (RUTF). RUTF is made according to a standard, energy-rich composition defined by the World Health Organization (WHO). The benefits of RUTF include a low moisture content, long shelf life without needing refrigeration and that it requires no preparation.

Objectives

To assess the effects of home-based RUTF on recovery, relapse and mortality in children with severe acute malnutrition.

Search methods

We searched the following electronic databases up to April 2013: Cochrane Central Register of Clinical Trials (CENTRAL), MEDLINE, MEDLINE In-process, EMBASE, CINAHL, Science Citation Index, African Index Medicus, LILACS, ZETOC and three trials registers. We also contacted researchers and clinicians in the field and handsearched bibliographies of included studies and relevant reviews.

Selection criteria

We included randomised and quasi-randomised controlled trials where children between six months and five years of age with severe acute malnutrition were treated at home with RUTF compared to a standard diet, or different regimens and formulations of RUTFs compared to each other. We assessed recovery, relapse and mortality as primary outcomes, and anthropometrical changes, time to recovery and adverse outcomes as secondary outcomes.

Data collection and analysis

Two review authors independently assessed trial eligibility using prespecified criteria, and three review authors independently extracted data and assessed trial risk of bias.

Main results

We included four trials (three having a high risk of bias), all conducted in Malawi with the same contact author. One small trial included children infected with human immunodeficiency virus (HIV). We found the risk of bias to be high for the three quasi-randomised trials while the fourth trial had a low to moderate risk of bias. Because of the sparse data for HIV, we reported below the main results for all children together.

RUTF meeting total daily requirements versus standard diet

When comparing RUTF with standard diet (flour porridge), we found three quasi-randomised cluster trials ($n = 599$). RUTF may improve recovery slightly (risk ratio (RR) 1.32; 95% confidence interval (CI) 1.16 to 1.50; low quality evidence), but we do not know whether RUTF improves relapse, mortality or weight gain (very low quality evidence).

RUTF supplement versus RUTF meeting total daily requirements

When comparing RUTF supplement with RUTF that meets total daily nutritional requirements, we found two quasi-randomised cluster trials ($n = 210$). For recovery, relapse, mortality and weight gain the quality of evidence was very low; therefore, the effects of RUTF are unknown.

RUTF containing less milk powder versus standard RUTF

When comparing a cheaper RUTF containing less milk powder (10%) versus standard RUTF (25% milk powder), we found one trial that randomised 1874 children. For recovery, there was probably little or no difference between the groups (RR 0.97; 95% CI 0.93 to 1.01; moderate quality evidence). RUTF containing less milk powder may lead to slightly more children relapsing (RR 1.33; 95% CI 1.03 to 1.72; low quality evidence) and to less weight gain (mean difference (MD) -0.5 g/kg/day; 95% CI -0.75 to -0.25; low-quality evidence) than standard RUTF. We do not know whether the cheaper RUTF improved mortality (very low quality evidence).

Authors' conclusions

Given the limited evidence base currently available, it is not possible to reach definitive conclusions regarding differences in clinical outcomes in children with severe acute malnutrition who were given home-based ready-to-use therapeutic food (RUTF) compared to the standard diet, or who were treated with RUTF in different daily amounts or formulations. Well-designed, adequately powered pragmatic randomised controlled trials of HIV-uninfected and HIV-infected children with severe acute malnutrition are needed.

PLAIN LANGUAGE SUMMARY

Ready-to-use therapeutic food as home-based treatment for severely malnourished children between six months and five years old

Malnourished children have a higher risk of death and illness. Treating severely malnourished children in hospitals is not always desirable or practical in rural settings, and home treatment may be better. Home treatment can be food prepared by the carer, such as flour porridge, or commercially manufactured food such as ready-to-use therapeutic food (RUTF). RUTF is made according to a standard, energy-rich composition defined by the World Health Organization. Typically, RUTF is made from full-fat milk powder, sugar, peanut butter, vegetable oil, and vitamins and minerals. The benefits of RUTF include a low moisture content, a long shelf life without needing refrigeration and that it requires no preparation.

We assessed RUTF compared with a standard diet (flour porridge) for treatment, and examined whether a cheaper RUTF treatment (smaller amounts or using cheaper ingredients) can achieve similar health outcomes in severely malnourished children between six months and five years old. The main health outcomes that we investigated were recovery from severe malnutrition, relapse (getting more malnourished), death and weight gain.

We carried out a comprehensive search of trials up to April 2013 and found four studies. All studies were conducted in Malawi, with one small study that included children infected with human immunodeficiency virus (HIV). The extent to which results of the studies can be believed based on how the studies were done was poor for three studies, while the fourth study had stronger methods. Because of the sparse data for HIV, we report the main results for all children together.

For RUTF given as a total dietary replacement compared to flour porridge, we found three studies with 599 children. RUTF may improve recovery slightly, but we do not know whether RUTF improves relapse, death or weight gain as the quality of evidence was very low.

When comparing RUTF used as a supplement to their ordinary diet with RUTF used as a total dietary replacement, we found two small studies with 210 children. For recovery, relapse, death and weight gain, the quality of evidence was very low and, therefore, we do not know what the effects are.

When comparing a cheaper RUTF containing less milk powder (10%) with standard RUTF (25% milk powder), we found one study that randomised 1874 children. For recovery, there probably was little or no difference between the groups. RUTF containing less milk powder may lead to slightly more children relapsing and to less weight gain than standard RUTF. We do not know whether the cheaper RUTF reduces the number of children dying.

Current evidence is limited and, therefore, we cannot conclude that there is a difference between RUTF and flour porridge as home treatment for severely malnourished children, or between RUTF given in different daily amounts or with different ingredients. In order to determine the effects of RUTF, more high-quality studies are needed.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Patient or population: children aged 6 months to 5 years with severe acute malnutrition Settings: home-based Intervention: RUTF Comparison: standard diet						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard diet	RUTF				
Recovery Different definitions ¹ Follow-up: during intervention period	597 per 1000	788 per 1000 (693 to 896)	RR 1.32 (1.16 to 1.5)	599 (3 studies)	⊕⊕○○ low ^{2,3}	-
Relapse Admission to inpatient therapeutic care Follow-up: during intervention period	See comment	See comment	Not estimable	599 (3 studies)	⊕○○○ very low ^{2,3,4}	2 studies found a large effect with RUTF, 1 study did not detect an effect ⁵
Mortality Follow-up: during intervention period	54 per 1000	53 per 1000 (25 to 111)	RR 0.97 (0.46 to 2.05)	599 (3 studies)	⊕○○○ very low ^{2,3,6}	-
Weight gain (g/kg/day) Follow-up: first 4 weeks of intervention period	-	The mean weight gain in the intervention groups was 1.47 higher (0.49 to 2.45 higher)	-	595 (3 studies)	⊕○○○ very low ^{2,3,7,8}	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio; RUTF: ready-to-use therapeutic food.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ The three studies had different definitions for recovery. Ciliberto 2005: reaching WHZ > -2; Manary 2004: reaching WHZ $\geq$ 0; Ndekha 2005: reaching 100% weight for height.

² Downgraded by 1 for risk of bias: all studies had a high risk of bias for sequence generation and allocation concealment.

³ Downgraded by 1 for indirectness: all studies were carried out in the same country (Malawi) by a similar group of investigators. Therefore, generalisability to other countries is not assured.

⁴ Downgraded by 1 for inconsistency: studies are highly inconsistent and a meta-analysis is uninformative.

⁵ Manary 2004 and Ndekha 2005 had no relapses in the RUTF group, but 28 relapses with the standard diet group (RR 0.05, 95% CI 0.00 to 0.74, n = 182; RR 0.10, 95% CI 0.01 to 1.70, n = 65, respectively). Ciliberto 2005 found no effect (RR 0.55, 95% CI 0.24 to 1.26, n = 352). With such large differences in effect estimates, a meta-analysis is uninformative.

⁶ Downgraded by 1 for imprecision: the studies are too small to have full confidence in the effects. The 95% confidence interval of the meta-analysis ranges from 54% mortality reduction to doubling of mortality.

⁷ Not downgraded for inconsistency. Weight gain varied substantially between the three studies. The Chi² test did not demonstrate heterogeneity, but the analysis is quite underpowered.

⁸ Downgraded by 1 for imprecision: using the estimated MD (MD 1.47, 95% CI 0.49 to 2.45), we estimated for a child weighing 6 kg, over 30 days, mean weight gain would be 264 g (95% CI 88.2 to 441). Because the lower confidence interval estimate of 88.2 g is clinically insignificant we downgraded by 1.

BACKGROUND

Description of the condition

Malnutrition occurs when the quantity of one or more macronutrients available to body tissues is inadequate to sustain optimal bodily functions (Manary 2008), and this is usually accompanied by numerous micronutrient deficiencies. Malnutrition is a broad concept that includes a variety of clinical conditions such as kwashiorkor, marasmus, marasmic kwashiorkor, wasting or stunting, and micronutrient deficiencies. For the purpose of this review, the term malnutrition only refers to undernutrition. Macronutrient malnutrition is the focus of this review, so it includes all of the above conditions, which could also be accompanied by different degrees of micronutrient deficiencies.

Malnutrition commonly affects infants and young children, pregnant and lactating women, and elderly people. More than 77 million children are born every year in the 36 countries with the highest burden of malnutrition (21 of these countries are in Africa, 13 in Asia and two in Latin America) (Bhutta 2008; Black 2008). Of these children, about 7.4 million die before the age of three years and a further 0.6 million die between the ages of three and five years (Bhutta 2008). Short-term consequences of malnutrition include mortality and morbidity, for example, pneumonia, diarrhoea, fatigue and impaired thermoregulation (Black 2008). In the long term, malnutrition in children may affect adult size, intellectual ability, economic productivity and reproductive performance, and increase the risk of metabolic disorders and cardiovascular disease (Black 2008).

In children under five years of age, malnutrition can be classified as moderate or severe. Moderate malnutrition - often referred to as moderate acute malnutrition (MAM) - is defined as a weight for height z score (WHZ) between two and three standard deviations (SDs) below the mean. Severe malnutrition - often referred to as severe acute malnutrition (SAM) - is defined as a WHZ of more than three SDs below the mean, or a mid-upper arm circumference (MUAC) of less than 115 mm, or the presence of nutritional oedema (Collins 2003; Manary 2008; WHO and UNICEF 2009). MAM or SAM without bilateral pitting oedema is termed marasmus. In the presence of bilateral pitting oedema, the term kwashiorkor is used (Manary 2008). See Table 1 for a more detailed classification system for MAM and SAM.

Although some conditions may contribute to the onset of malnutrition (for example, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), tuberculosis (TB), kidney failure), poverty and food insecurity are major causes. Malnutrition and infection have a reciprocal effect since a lower host response to infection contributes to compromised nutritional status and vice versa (Kruger 2008; Naude 2008). Infections are associated with anorexia (loss of appetite) and decreased food intake; fever increases energy expenditure; and diarrhoea decreases nutri-

ent absorption; these result in wasting and higher mortality from infectious diseases (Kruger 2008; Naude 2008).

Description of the intervention

Ultimately, the only way to end malnutrition is to address economic deprivation and inequity. However, conditions can be mitigated by offering specific nutritional interventions (Black 2008). Hospitalised treatment for SAM children typically entails treatment with F75 (the starter milk-based therapeutic formula; thus referred to as phase 1 or stabilisation phase) (ACF International Network 2009; WHO and UNICEF 2009). During this stabilisation phase, the oedema (if present) starts to disappear, leading to weight loss (fluid loss). F75 aids in boosting the metabolism and restoring hydroelectric equilibrium (ACF International Network 2009). Next, F100 (a milk-based therapeutic diet; also called phase 2 treatment) is given to initiate weight gain.

Ready-to-use foods (RUF) are energy-dense food with a low moisture content that can be eaten directly from the packaging. When used for nutritional rehabilitation of children with SAM, such products are referred to as ready-to-use therapeutic food (RUTF). RUTF was originally developed as a home-based alternative to F100. RUTF, in the form of a solid or semi-solid feed, has a similar nutrient profile to F100 (except for the presence of iron) (Collins 2006; WHO 2007). Table 2 shows the nutritional contents of RUTF as recommended by the World Health Organization (WHO).

RUTF can either be commercially produced on large scale or produced locally (usually on small scale with ingredients that may differ slightly from commercially produced RUTF as these may be locally sourced). Two examples of commercially produced RUTF are a peanut-based paste called Plumpy'nut® (developed by Nutriset, Plumpy'nut, and the Institute for Research and Development, France) and a solid biscuit made from cooked wheat called BP100® (developed by Compact, Denmark) (Collins 2004; Navarro-Colorado 2005). Both are fortified with micronutrients and have very low water activity, which discourages microbial growth (Brewster 2006; WHO 2007; Kruger 2008). This is an important feature since clean safe water is not widely available in many poor communities. Children as young as six months can consume RUTF with a homogenous paste texture. Solid RUTF can be soaked in clean boiling water and eaten as porridge by such young children, or older children can consume it as a biscuit.

Communities can also learn how to produce their own RUTF, as in Malawi where a peanut-based RUTF is produced (Sandige 2010 [pers comm]). Table 3 shows a typical recipe for a peanut-based RUTF. Examples of other countries that manufacture RUTF are Ethiopia, Niger and the Democratic Republic of Congo in Africa, as well as Sri Lanka, Indonesia and Pakistan in Asia (DFID 2009). The manufacturing equipment and technology needed to produce RUTF is simple and can be transferred to any country with minimal industrial infrastructure (WHO 2007). The methods of

quality control that are needed and the exact cost are determined by the scale of production (Manary 2006), but on average RUTF costs approximately USD3 per kilogram when locally (non-commercially) produced (WHO 2007). In April 2012, we communicated with Nutriset and obtained their prices for Plumpy'nut®: EUR2.7 per kilogram (EUR0.25 for a 92g packet), which excludes transport and import tax cost. Children with SAM normally need 10 to 15 kg of RUTF given over a period of six to eight weeks for recovery from undernutrition (WHO 2007). Authors of a cost analysis in Ethiopia reported that the cost of commercially produced RUTF per child treated at home is USD128 while in a healthcare facility it is significantly more expensive at USD262 (Tekeste 2012). In an analysis conducted in Zambia, the authors reported a cost of USD202 per child for home-based RUTF treatment when compared to no treatment (Bachmann 2009). Studies comparing the costs of RUTF with standard home-based treatment (for example, a porridge made from a maize and soy flour blend) are not available.

Recipes for RUTF do not necessarily include peanut or milk powder, although the WHO recommends that at least half of the proteins should come from a milk source (WHO 2007). Peanuts can cause allergic reactions in susceptible individuals and are known to have a high risk for aflatoxin contamination. Milk powder is expensive and often has to be imported (Collins 2004). The cost of milk powder in Malawi constitutes more than half of the cost of the final RUTF (Collins 2004). For non-commercial production of RUTF, the following basic ingredients should be present (Collins 2004).

- A staple food as the main ingredient (preferably a cereal).
- A protein supplement from a plant or animal food (for example, beans, groundnuts, milk, meat, chicken, fish, egg). To make the production of RUTF cost-effective, legumes and oilseeds are mostly used.
- A vitamin and mineral supplement (a vegetable or fruit, or both).
- An energy supplement (a fat, oil or sugar) to increase the energy density.

The food safety of the production process should be strictly monitored, with careful attention given to avoid contamination by microorganisms or other harmful substances (for example, heavy metals, pesticides, anti-nutritional factors such as phytate or protease inhibitors) (WHO 2007). Table 4, Table 5 and Table 6 give three recipes for locally produced RUTF. Table 7, Table 8 and Table 9 provide nutritional information and water activity of these recipes as well as for Plumpy'nut®.

How the intervention might work

Adequate energy, protein and micronutrient intake is vital for maintaining a functioning immune system or restoring a system that is dysfunctional (Naude 2008). Malnutrition is a condition

where the body is in great need of nutrients. Individuals recovering from malnutrition require relatively large amounts of nutrients, in particular energy. Infants and young children have a small body size, which limits the amount of food that can be given in a single feed (Lin 2008). Lower energy-density foods, together with a low frequency of feeding, can result in an energy intake that is insufficient to enable recovery.

The following characteristics of RUTF may contribute to its possible beneficial effect in the treatment of malnutrition.

- Balanced, nutritious, home-based therapy.
- Affordable compared to facility-based care.
- Can be eaten safely at home, even where hygienic conditions are poor (WHO 2007).
- Long shelf life.
- No special storage (for example, refrigeration) or preparation required.

Why it is important to do this review

The vast majority of children with malnutrition live in low- and middle-income countries (LMIC). Many of these children never visit healthcare facilities (WHO 2007; Black 2008) due to reasons such as a lack of money for transport to facilities or long travel distances, or both; parents' lack of health status awareness; and a lack of healthcare resources to treat thousands of malnourished children in facilities (Kruger 2008). Furthermore, hospital admission exposes people with uncomplicated SAM to additional risks of nosocomial infections and takes the mother or carer away from other children for prolonged periods, which may increase the risk for sibling malnutrition (Collins 2003). Therefore, an alternative treatment for severe uncomplicated malnutrition may be a home-based nutritional intervention, such as RUTF, which does not require specialised healthcare personnel and expensive equipment (Kruger 2008).

Both the WHO and the United Nations Children's Fund (UNICEF) now recommend the use of RUTF in the community as therapeutic feeding for children with SAM (WHO and UNICEF 2009) (see Table 10). The findings of this systematic review will be of significant value to people in LMIC as well as to organisations involved in preparing clinical guidelines for practitioners and policy makers in LMIC (for example, WHO, UNICEF and government health departments).

OBJECTIVES

To assess the effects of home-based RUTF on recovery, relapse, mortality, time to recovery and anthropometrical changes in children with SAM. Specific comparisons investigated were:

- RUTF meeting total daily nutritional requirements versus standard diet (for example, flour porridge);
- RUTF supplement versus RUTF meeting total daily nutritional requirements;
- RUTF containing less milk powder versus standard RUTE.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including those defined as quasi-randomised (that is, trials that used an inadequate method of randomisation, such as alternation or date of birth). We also included cluster randomised trials (that is, trials randomised by groups such as schools, villages or families).

Types of participants

Children between six months and five years of age with SAM, regardless of country, setting or disease status and irrespective of the method of diagnosis employed.

Types of interventions

Experimental

- RUTF as defined by the study authors (either commercially or non-commercially produced).

Control

- Alternative RUTF type (for example, corn/soy-based versus peanut-based, reduced milk powder content).
- Treatment as usual (for example, standard diet).

Any trial in which the effects of an RUTF were potentially confounded by another intervention was excluded, that is, where multiple interventions were involved, comparison groups should have received the same treatment apart from the experimental RUTE.

Types of outcome measures

Primary outcomes

- Recovery as defined by the study authors.
- Deterioration or relapse during and beyond the intervention period as defined by the study authors.
- Mortality.

Secondary outcomes

- Mean weight gain per kilogram body weight per day during the intervention period.
- Time to recovery (duration to rehabilitation).
- Anthropometrical status at all reported time points during and beyond the intervention period (for example, WHZ, weight for age z score (WAZ), height for age z score (HAZ), MUAC).
- Cognitive function and development during the intervention period (for example, Denver Developmental Screening Test, Bayley Scales of Infant Development).
- Adverse outcomes as reported by investigators (for example, allergic reactions, refusal of feeds due to poor palatability, diarrhoea).

Search methods for identification of studies

We used a comprehensive search strategy to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

We searched the following electronic sources up to April 2013 to identify relevant studies that assessed the effects of RUTF on malnutrition.

- The Cochrane Central Register of Clinical Trials (CENTRAL), 2013, Issue 3, searched 4 April 2013
- Ovid MEDLINE 1946 to March week 4 2014, searched 4 April 2013
- EMBASE 1980 to 2013 week 13, searched 4 April 2013
- African Index Medicus, searched 8 April 2013
- CINAHL 1937 to current, searched 8 April 2013
- Science Citation Index 1970 to 3 April 2013, searched 4 April 2013
- LILACS, searched 8 April 2013
- ZETOC (limited to conference search), searched 8 April 2013
- ClinicalTrials.gov (clinicaltrials.gov/), searched 8 April 2013
- Current Controlled Trials (www.controlled-trials.com/), searched 8 April 2013
- WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), searched 8 April 2013

[Appendix 1](#) shows the complete search histories for each database.

Searching other resources

In order to obtain additional references, we contacted researchers, paediatricians and community dietitians. We scrutinised the reference lists of included studies and appropriate reviews in order to identify relevant studies. We contacted the authors of each trial identified in the trial registries to establish whether the trial had already been published, and the authors of all included studies to

determine if they were aware of additional trials (published, unpublished or ongoing) in the field.

Data collection and analysis

Selection of studies

Two review authors (AS and ML) independently screened the title and abstract of studies identified by the search and applied the prespecified eligibility criteria in order to identify relevant studies. Where at least one review author considered a study to be relevant we obtained the full text and independently assessed it for eligibility. We contacted the authors of the primary studies where there was missing information or clarification was needed. We resolved any remaining disagreements by consensus among the review authors. We listed studies first thought to be relevant but which we later excluded in the [Characteristics of excluded studies](#) with reasons for exclusion.

Data extraction and management

Three review authors (AS, ML and AM) independently extracted data using a standardised, pre-piloted data extraction form and resolved disagreements by consensus among the review authors. For each relevant study, we extracted the following: source (for example, contact details and citation); methods (for example, ethics approval and study design); participants (for example, age and comorbidity); interventions (for example, description, dose and duration); outcomes (for example, description and time point(s) collected); results (for example, number of participants randomised per arm and numerical results for prespecified outcomes); safety (for example, number and description of adverse effects or events per arm) and miscellaneous information (for example, funding source and references to other relevant studies).

We contacted the study authors where reported information was unclear or contradictory, or where important data were missing. We entered the extracted data into one of the following three tables: (1) [Characteristics of included studies](#), (2) [Characteristics of excluded studies](#) and (3) [Characteristics of ongoing studies](#).

Assessment of risk of bias in included studies

Three review authors (AS, ML and AM) independently assessed each included study for risk of bias using the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) using the specific criteria in [Appendix 2](#). The assessed domains were adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other potential sources of bias. We rated each included study as low risk of bias, high risk of bias or unclear risk of bias according to each of the six domains. We discussed disagreements with a fourth review author (JV).

We evaluated cluster-randomised trials according to the following criteria: recruitment bias, baseline imbalance and loss of clusters (Higgins 2008), using the specific criteria shown in [Appendix 3](#).

Measures of treatment effect

We used Review Manager 5 (RevMan) to manage the data and to conduct the analysis (RevMan 2011). We calculated risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data. We presented all results with 95% confidence intervals (CI).

Unit of analysis issues

Because of the nature of SAM, we did not expect to find any cross-over trials.

For cluster-randomised trials, we followed the method of adjusting for clustering as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). None of the three included cluster-randomised trials had properly accounted for the cluster design. Therefore, we used an 'approximate method', which entailed calculation of an 'effective sample size' for the comparison groups by dividing the original sample size by the 'design effect', which is $1 + (c-1)ICC$, where c is the average cluster size and ICC is the intracluster correlation coefficient. For dichotomous data, we divided both the number of participants and the number who experienced the event by the same design effect, while for continuous data, only the sample size was reduced (means and SDs were left unchanged). The required information was available for two of the cluster-randomised trials and we contacted the study author of the third trial to obtain the number of clusters. We imputed a low ICC of 0.001 for two studies because we did not anticipate large between-cluster variability. The clusters in these studies were either the number of weeks of discharge or the days of discharge in the month. In this way, children from the same community were assessed in the same facility. We imputed a higher ICC of 0.005 for the third study because seven different facilities represented seven clusters. We, therefore, expected a certain degree of between-cluster variability in this study. Although the values are relatively arbitrary, we preferred to use them to adjust the sample sizes due to the implausibility of an ICC of 0. We had initially intended to use the generic inverse variance method in RevMan, but since we had values for the totals, means and SDs per group from each study for continuous data, it became unnecessary to do so.

Two studies had two treatment arms that were compared to the same control (Manary 2004; Ndekha 2005). The one treatment arm received sufficient RUTF to meet daily nutritional requirements whereas the second treatment arm received RUTF supplementary to their habitual diet. Therefore, these two treatments were such that the arms could not be combined into a single pairwise comparison (Higgins 2008). As these two different treatment arms relate to different research questions (see the three subsections in [Effects of interventions](#) section) they were analysed separately.

In Comparison 1, we thus selected the arm that received RUTF in sufficient quantity to meet daily nutritional requirements and compared the results of this arm with the results of the full control group (only considering the ICC). In Comparison 2, we selected the arm that received RUTF as a supplement and compared the results of this arm with the results of the full control group (only considering the ICC).

We reported data of all collection time points during and after the intervention period (follow-up) as stipulated in the 'Types of outcomes' section (unless otherwise stated). We could not group time points as planned owing to the data obtained (one month or less of RUTF treatment, less than one to two or more months of RUTF treatment and more than two to six months of RUTF treatment). The primary outcomes were either measured at the time of recovery (which varied between participants and such individual data were not reported unless time to recovery was an outcome in the study), or at the end of a predetermined time period. We did not distinguish in the analyses between such studies; however, we reported what time points were used with each outcome in each study.

Dealing with missing data

We classified important missing data per study as (1) pre-randomisation, (2) immediately post-randomisation or (3) drop-outs during the intervention phase, alongside reasons for the absence where these were reported in the article (Table 11). We attempted to obtain essential missing data by contacting the study authors via email. We imputed values for ICC because we could not obtain them from published data.

For dichotomous data (for example, recovery and mortality during the intervention period), we used the intention-to-treat (ITT) principle to calculate effect sizes for individual studies or to pool more than one study. We assumed that the participants who were loss to follow-up or dropped out of the study did not experience the event of interest. However, for the outcome 'relapse' we assumed that those who dropped out did not receive any treatment (RUTF or standard diet) and, therefore, experienced the event. Furthermore, when assessing dichotomous outcomes (for example, recovery) at *follow-up* (for example, six months after the children initially recovered) we employed the available-case principle, that is, only those who recovered during the intervention period and came back for follow-up were assessed as opposed to all children who recovered. We consider it is not plausible to assume that those who did not come back deteriorated. For continuous data, we calculated MDs for studies based on the available-case principle.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of forest plots and statistically by means of the Chi^2 test for heterogeneity (significance level P value < 0.1). We quantified heterogeneity using the

I^2 test (Higgins 2002) where I^2 values of 50% or more indicated a substantial level of heterogeneity (Higgins 2003).

Assessment of reporting biases

We had planned to assess the likelihood of reporting bias with funnel plots using at least 10 studies per outcome (Higgins 2008). However, we included only four studies.

Data synthesis

We anticipated a high degree of heterogeneity due to the inclusion of children with a variety of conditions related to malnutrition (for example, marasmus, kwashiorkor, stunting) and various types of RUTF (for example, corn/soy-based RUTF, peanut-based RUTF). For this reason, we used a random-effects model to combine the results where appropriate. Where substantial statistical heterogeneity existed, we did not pool study results in a meta-analysis but reported effect sizes per study separately. We evaluated the quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool (Guyatt 2011).

Subgroup analysis and investigation of heterogeneity

We intended to compare the intervention effects across the following subgroups:

- different types of RUTF products (for example, corn/soy-based versus peanut-based RUTF);
- age of children: 6 to 12 months, as this is the ideal period to start weaning from a milk-based diet; 13 months to 5 years, as these children consume a mixed diet (mostly not breast milk although the child may still be taking some);
- children with or without comorbid disease (for example, HIV/AIDS, TB, malaria).

The available data, however, allowed us to conduct subgroup analyses only for HIV status.

Sensitivity analysis

We had planned to perform sensitivity analyses; however, since we only identified four studies, we deemed sensitivity analyses inappropriate. In future updates it may be feasible to assess the influence of study quality (using adequacy of allocation concealment as a marker) and study design (for example, cluster-randomised controlled trials versus individually randomised controlled trials) on the findings.

RESULTS

Description of studies

Results of the search

We summarised the search results in detail in [Figure 1](#). Briefly, we screened 2830 records of which we identified 26 as potentially eligible. Scrutinising the 26 full-text articles resulted in four studies meeting our eligibility criteria; we excluded the remainder for the reasons displayed in the [Characteristics of excluded studies](#) table. We identified six ongoing studies, the available details of which are provided in the [Characteristics of ongoing studies](#) table. We entered non-English abstracts into Google Translate to get a general idea of the study details. We did not need to obtain the full text for any non-English study.

Figure 1. Flow diagram of search.

Included studies

We included four trials with 2894 children. All four studies were conducted in Malawi by a similar group of investigators (that is, same contact author and a number of co-authors overlap). The articles [Manary 2004](#) and [Ndekha 2005](#) come from the same trial, but we included them as separate studies as they involved different children, namely with and without HIV. Three of the trials were cluster-randomised. Using the effective sample size for the cluster-randomised trials, the total number of children included in this review is 2594. Below is the list of included studies grouped according to the type of comparison. The [Characteristics of included studies](#) table provides further details.

Comparison 1: RUTF meeting total daily requirements versus standard diet (flour porridge)

- [Ciliberto 2005](#): quasi-randomised cluster trial of 645 children with an effective sample size of 352 (HIV status not reported), aged between 10 and 60 months were assessed in Malawi. The RUTF was locally manufactured and the standard diet provided first in hospital and then at home.
- [Manary 2004](#): quasi-randomised cluster trial of 186 HIV-uninfected children (effective sample size 181) older than 12 months of age were assessed in Malawi. The RUTF was commercially produced.
- [Ndekha 2005](#): quasi-randomised cluster trial of 65 HIV-infected children (effective sample size 65) aged between 12 and 60 months were investigated in Malawi. The RUTF was commercially produced.

Comparison 2: RUTF supplement versus RUTF meeting total daily requirements

- [Manary 2004](#): quasi-randomised cluster trial of 165 HIV-uninfected children (effective sample size 161) older than 12 months of age were assessed in Malawi. The RUTF was commercially produced.
- [Ndekha 2005](#): quasi-randomised cluster trial of 48 HIV-infected children (effective sample size 48) aged between 12 and 60 months were investigated in Malawi. The RUTF was commercially produced.

Comparison 3: RUTF containing less milk powder versus standard RUTF

- [Oakley 2010](#): individually randomised trial of 1874 children (those known to be HIV-infected were excluded from the trial) aged between 6 and 59 months in Malawi. RUTF was locally produced.

As the children of all included studies were severely malnourished, the interventions in three studies were given after the children had been stabilised with F75. [Oakley 2010](#) did not report on stabilisation. All studies provided peanut-based RUTF. The two studies that involved commercially produced RUTF used Plumpy'nut® (manufactured by Nutriset, Malaunay, France).

While we would have liked to report on the change (gain) in symptoms or signs from baseline for all continuous outcomes, this was not always possible as studies did not provide the information required to calculate this (for example, values at baseline and SD of change). In such cases, we assessed the difference in outcomes at the end of the intervention period. This is not an ideal approach given that the studies were generally small (effective sample sizes ranging from 93 to 1874; median 314) and only one was adequately randomised. The outcomes are solely dependent on anthropometrical measurements. Only one study sufficiently described how measurements were done allowing the reader to judge the quality (see the [Characteristics of included studies](#) table) ([Oakley 2010](#)).

Excluded studies

We excluded 22 studies. The most common reasons for exclusion were that the intervention was not a RUTF (seven studies) and that the study design was neither an RCT nor a quasi-randomised trial (six studies). Furthermore, three studies only included moderately malnourished children; two were not home-based; two compared commercially produced RUTF with non-commercially produced RUTF; one looked at prevention (and not treatment), and one study examined the acceptability of RUTF rather than the efficacy or safety, or both. (See the [Characteristics of excluded studies](#) table.)

Risk of bias in included studies

We present our judgements regarding the risk of bias in each of the included studies in the [Characteristics of included studies](#) table. We found the risk of bias to be high for the three quasi-randomised trials while the fourth trial had a low to moderate risk of bias. Two figures provide a graphical summary of the risk of bias assessments ([Figure 2](#); [Figure 3](#)). We present additional information regarding the risk of bias in the three cluster-randomised trials in [Table 12](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ciliberto 2005						
Manary 2004						
Ndekha 2005						
Oakley 2010						

Allocation

Allocation refers to both the generation of the random allocation sequence and concealment of the allocation code.

We judged one included study to have a low risk of selection bias (Oakley 2010); the other three studies were quasi-randomised and, therefore, we judged them to have a high risk of selection bias.

Blinding

We judged all four included studies to have a low risk of performance bias because the participants across groups received the

same amount of contact time with study personnel. In terms of detection bias, only Oakley 2010 reported that outcome assessors were unaware of the intervention that the child received. However, it was not explained how blinding was ensured. In Ciliberto 2005, outcome assessors were not blinded, and in Manary 2004 and Ndekha 2005, blinding was not reported. As the majority of the primary and secondary outcomes were dependent on physical measurements by outcome assessors, we judged all included studies to have an unclear risk of detection bias.

Incomplete outcome data

We judged two studies to have a low risk of attrition bias as they did not have different losses to follow-up in the two groups or large numbers of losses to follow-up (Ciliberto 2005; Oakley 2010). We judged the other two studies to have a high risk of bias (Manary 2004; Ndekha 2005) due to different losses to follow-up between the two treatment groups. It is worth noting that these two studies both had three arms: RUTF (total daily requirements), RUTF supplement and standard diet (flour porridge). In both these studies, the RUTF supplement arm had more than double the percentage attrition than the other two arms. We provided a summary of missing data in Table 11.

Selective reporting

For each included study, we searched for the protocol in the trial registries mentioned under Search methods for identification of studies and contacted the primary study authors asking whether their studies had been registered. Studies for which no protocol was available can at best be judged as having an unclear risk of bias with regards to selective reporting. This was the case in all studies except for Oakley 2010, which was registered. For the three included studies without a registered protocol, we assessed whether reports provided the prespecified study outcomes in the Methods section and judged those that did not specify their outcomes as having a high risk of bias. Ciliberto 2005 and Manary 2004 prespecified their outcomes and addressed them adequately; hence we judged them to have an unclear risk of bias. We judged studies that reported results for outcomes in addition to the prespecified outcomes, or those that prespecified outcomes but did not report such results, to have a high risk of bias (Ndekha 2005; Oakley 2010).

Other potential sources of bias

We judged Oakley 2010 to have a low risk of bias as the baseline characteristics in the two groups were similar, and the study was not funded by industry. In terms of baseline characteristics, we judged two studies to have an unclear risk of bias because there were significant differences in important baseline characteristics between the treatment and control groups (Ciliberto 2005; Ndekha 2005). We judged two studies in which a commercial RUTF manufacturer donated RUTF to have an unclear risk of bias (Manary 2004; Ndekha 2005). Furthermore, where there was risk of differential sharing of interventions by non-participants (siblings and other family members) between comparison groups we considered this a further potential source of bias. We identified the studies by Manary 2004 and Ndekha 2005 as having a risk of such sharing.

In cluster-randomised trials, it is important to consider the unit of randomisation to avoid potential bias. We investigated this for the three cluster-randomised trials (Manary 2004; Ciliberto 2005;

Ndekha 2005). None of these studies calculated the effective sample size or accounted for clustering in their analyses. In addition, we assessed recruitment bias, cluster baseline imbalances and loss of clusters for these three studies (Table 12). We judged two studies (Manary 2004; Ndekha 2005) to have a low risk of recruitment bias because, although the children were recruited after the different clusters were allocated a specific intervention, an independent doctor discharged the children without knowing which discharge days matched which intervention. We judged one study (Ciliberto 2005) to have a high risk of recruitment bias because children were recruited after sites were assigned a specific intervention. In terms of baseline imbalances, we judged all three cluster-randomised trials to have an unclear risk of bias because no relevant information was provided to assess this particular aspect. All clusters in the three cluster-randomised trials were retained and, therefore, we judged them to have a low risk of bias regarding loss of clusters.

Effects of interventions

See: [Summary of findings for the main comparison](#) Ready-to-use therapeutic food (RUTF) compared to standard diet for children aged six months to five years with severe acute malnutrition; [Summary of findings 2](#) Ready-to-use therapeutic food (RUTF) supplement compared to RUTF (total daily requirements) for children aged six months to five years with severe acute malnutrition; [Summary of findings 3](#) Ready-to-use therapeutic food (RUTF) containing less milk powder compared to standard RUTF for children aged six months to five years with severe acute malnutrition

We were unable to analyse results by different age groups. There was no measurement of our secondary outcome, cognitive function and development, in any of the four trials. There was also no explicit measuring of allergic reactions as an adverse outcome.

Comparison 1: RUTF meeting total daily requirements versus standard diet (flour porridge)

Three trials with 896 children (effective sample size 598) evaluated the efficacy of RUTF versus flour porridge (Manary 2004; Ciliberto 2005; Ndekha 2005). All three trials assigned their participants in clusters, and all three were quasi-randomised trials. While Ciliberto 2005 did not report on the participants' HIV status, Manary 2004 mentioned that they only included HIV-uninfected children and Ndekha 2005 studied only HIV-infected children. For the analyses below, we grouped HIV-uninfected and HIV-untested children and referred to them as HIV-uninfected.

Primary outcomes

Recovery

Ciliberto 2005, Manary 2004 and Ndekha 2005 defined recovery as reaching a WHZ score > -2 , having a WHZ score ≥ 0 and reaching 100% weight for height, respectively. More children recovered with RUTF than with standard diet irrespective of HIV status (RR 1.32; 95% CI 1.16 to 1.50; $n = 599$) (Analysis 1.1; Figure 4) and there was no significant heterogeneity detected between the studies ($\text{Chi}^2 = 1.59$, degrees of freedom (df) = 2; P

value = 0.45; $I^2 = 0\%$). After excluding Ndekha 2005, where all participants were confirmed to be HIV-infected, the findings of the HIV-uninfected subgroup remained similar (RR 1.32; 95% CI 1.10 to 1.58; $n = 534$) and there was no significant heterogeneity between the trials ($\text{Chi}^2 = 1.49$, df = 1; P value = 0.22; $I^2 = 33\%$). In the HIV-infected subgroup (Ndekha 2005), there was no difference between the RUTF and standard diet groups (RR 1.41; 95% CI 0.97 to 2.04; $n = 65$).

Figure 4. Forest plot of comparison: I RUTF versus standard diet, outcome: I.1 Recovery.

Relapse

Relapse was defined as admission to inpatient therapeutic care during the study period (Manary 2004; Ciliberto 2005; Ndekha 2005). In Manary 2004, results were reported as “died or relapsed”. We contacted the study authors who sent us the data for “relapsed” and “died” separately. Due to heterogeneity ($\text{Chi}^2 = 5.58$; df = 2; P value = 0.06; $I^2 = 64\%$), we did not pool results for these three trials (Analysis 1.2). This heterogeneity could not be explained by subgroup analysis as the two trials where children were HIV-uninfected also had significant heterogeneity ($\text{Chi}^2 = 4.31$; df = 1; P value = 0.04; $I^2 = 77\%$). The RRs for Ciliberto 2005 and Manary 2004 were 0.55 (95% CI 0.24 to 1.26; $n = 352$) and 0.05 (95% CI 0.00 to 0.74; $n = 182$), respectively. RUTF was not favoured compared to standard diet in HIV-infected children (RR

0.10; 95% CI 0.01 to 1.70; $n = 65$) (Ndekha 2005).

Mortality

We detected no difference in mortality between the RUTF and standard diet groups (RR 0.97; 95% CI 0.46 to 2.05; $n = 599$) (Analysis 1.3; Figure 5), with no significant heterogeneity detected between the trials ($\text{Chi}^2 = 1.5$; df = 2; P value = 0.47; $I^2 = 0\%$) (Manary 2004; Ciliberto 2005; Ndekha 2005). Subgroup results for HIV-uninfected children (RR 0.78; 95% CI 0.32 to 1.88; $n = 534$) (Manary 2004; Ciliberto 2005) (no significant heterogeneity detected between the trials, $\text{Chi}^2 = 0.66$; df = 1; P value = 0.42; $I^2 = 0\%$) did not differ from subgroup results for children diagnosed with HIV (Ndekha 2005) (RR 1.69; 95% CI 0.42 to 6.85; $n = 65$).

Figure 5. Forest plot of comparison: I RUTF versus standard diet, outcome: I.3 Mortality.

Secondary outcomes

Weight gain

Manary 2004, Ciliberto 2005 and Ndekha 2005 reported weight gain measured during the first four weeks of the intervention period. We obtained data on weight gain from the contact author of Manary 2004 and pooled the results of the three trials. We found that the RUTF group gained more weight when compared to the standard diet group (MD 1.47 g/kg/day; 95% CI 0.49 to 2.45; n

= 595) (Analysis 1.4; Figure 6) and there was no significant heterogeneity detected between the trials ($\chi^2 = 2.92$; $df = 2$; P value = 0.23; $I^2 = 32\%$). When separating these results in subgroup analyses by HIV status, there was also a difference favouring RUTF in HIV-uninfected children (MD 1.79 g/kg/day; 95% CI 0.65 to 2.93; $n = 530$) (Manary 2004; Ciliberto 2005) and there was no significant heterogeneity detected between the trials ($\chi^2 = 1.28$; $df = 1$; P value = 0.26; $I^2 = 22\%$). However, in the subgroup of HIV-infected children, RUTF was not favoured above standard diet (MD 0.80 g/kg/day; 95% CI -0.64 to 2.24; $n = 65$) (Ndekha 2005).

Figure 6. Forest plot of comparison: I RUTF versus standard diet, outcome: I.4 Weight gain (g/kg/day).

Time to recovery

Ndekha 2005 measured time to recovery and reported results in median days. HIV-infected children in the RUTF group ($n = 20$) recovered within a median of 71 days (interquartile range 42 to 125) compared to 85 days (interquartile range 46 to 239) for the standard diet group ($n = 45$). The authors did not report a P value or significance for the difference in time to recovery between these two groups. Manary 2004 also reported time to recovery but results were displayed only in a graph from which accurate information could not be obtained for further analysis. We contacted the trial authors, who provided us with the necessary information. No difference in time to recovery was detected in HIV-uninfected children between the treatment and standard diet groups (MD -7.0 days; 95% CI -15.89 to 1.89; $n = 136$) (Analysis 1.5).

Mid-upper arm circumference (MUAC) gain

Three trials measured MUAC during the first four weeks of the intervention period. Data in Manary 2004 were reported only in graph form and we obtained the actual values from the contact author. We found that children in the RUTF group had a higher MUAC gain compared to children with standard diet (MD 0.13 mm/day; 95% CI 0.04 to 0.21; $n = 570$) (Analysis 1.6) and there was no significant heterogeneity detected between trials in all children ($\text{Chi}^2 = 2.3$; $\text{df} = 2$; P value = 0.32; $I^2 = 13\%$). After excluding results for children with HIV, a subgroup analysis of the HIV-uninfected subgroup also found a higher MUAC gain with RUTF compared with standard diet (MD 0.15 mm/day; 95% CI 0.07 to 0.24; $n = 505$) (Manary 2004; Ciliberto 2005) and there was no significant heterogeneity between the trials ($\text{Chi}^2 = 0.05$; $\text{df} = 1$; P value = 0.82; $I^2 = 0\%$). In the HIV-infected subgroup, however, we detected no difference between RUTF and standard diet (MD -0.04 mm/day; 95% CI -0.28 to 0.20; $n = 65$) (Ndekha 2005).

Weight for height z score (WHZ)

HIV-uninfected children who recovered and were discharged from the trial were followed up for six months (Manary 2004). We obtained results from the contact author. There was no difference detected in WHZ between the RUTF and standard diet group (MD 0.19; 95% -0.22 to 0.60; $n = 99$; Analysis 1.7). We could not report on WHZ gain because the SD of change or the exact P value of the difference between the change in each group were not reported. Since baseline values for WHZ across the different

groups were similar, results for WHZ gain would not have been different from the WHZ that we reported above.

Adverse outcomes

The numbers of days of diarrhoea per group were measured during the first two weeks of the treatment period (Ciliberto 2005). Children who received RUTF had a similar frequency of diarrhoea to those on standard diet (MD -0.6; 95% CI -1.30 to 0.10; $n = 352$) (Analysis 1.8). Ndekha 2005 measured the “prevalence of diarrhoea” (days of diarrhoea divided by the “total days” during the first two weeks of the treatment period) in HIV-infected children. Children in the RUTF group had diarrhoea on 19 out of the 304 evaluated days compared to 57 out of 687 evaluated days in children in the standard diet group. Since the corresponding numbers of participants were not reported, a treatment effect could not be calculated.

Comparison 2: RUTF supplement versus RUTF meeting total daily requirements

Two quasi-randomised cluster trials that used systematic sequence generation methods had the following three arms: (1) RUTF meeting total daily nutritional requirements, (2) the same RUTF given supplementary to children’s habitual diet and (3) standard diet (maize/soy flour) (Manary 2004; Ndekha 2005). Below we compared the RUTF (total daily requirements) with RUTF supplement. It is also important to note that Manary 2004 included only HIV-uninfected children while Ndekha 2005 only assessed HIV-infected children.

Primary outcomes

Recovery

Children who received the supplement were less likely to recover than those who received RUTF (RR 0.71; 95% CI 0.60 to 0.84; $n = 210$) (Manary 2004; Ndekha 2005) (Analysis 2.1; Figure 7) and there was no significant heterogeneity detected between the trials ($\text{Chi}^2 = 0.37$; $\text{df} = 1$; P value = 0.54; $I^2 = 0\%$). We made the same conclusion when considering HIV-uninfected and HIV-infected children in subgroups separately (RR 0.72; 95% CI 0.60 to 0.87; $n = 162$ for Manary 2004 and RR 0.62; 95% CI 0.39 to 0.99; $n = 48$ for Ndekha 2005).

Figure 7. Forest plot of comparison: 2 RUTF (total daily requirements) versus RUTF supplement, outcome: 2.1 Recovery.

Relapse

Manary 2004 and Ndekha 2005 measured relapse (admission to hospital) during the intervention period. Pooled results indicated that children were more likely to have relapsed in the supplement group (13 out of 122 children) when compared to the RUTF group where none of the 88 children relapsed (RR 8.95; 95% CI 1.18 to 67.77; n = 210) (Analysis 2.2; Figure 8). There was no significant heterogeneity between the trials (Chi² = 0.3; df = 1; P value = 0.58; I² = 0%). However, when separating the results into subgroups based on HIV status, there was no difference detected between the two groups (RR 15.25; 95% CI 0.91 to 255.9; n = 162; (Manary 2004) and RR 5.07; 95% CI 0.28 to 93.0; n = 48 (Ndekha 2005)).

Figure 8. Forest plot of comparison: 2 RUTF (total daily requirements) versus RUTF supplement, outcome: 2.2 Relapse.

Mortality

When comparing the supplement group with the RUTF group (Manary 2004; Ndekha 2005), we detected no difference in mortality (RR 0.73; 95% CI 0.25 to 2.18; n = 210) (Analysis 2.3; Figure 9) and there was no significant heterogeneity between the trials (Chi² = 0.36; df = 1; P value = 0.55; I² = 0%). Similarly, we detected no difference in mortality when assessing results for the HIV-uninfected (Manary 2004) and HIV-infected (Ndekha 2005) subgroups separately (RR 0.48; 95% CI 0.08 to 2.81; n = 162 and RR 0.95; 95% CI 0.24 to 3.80; n = 48, respectively).

Figure 9. Forest plot of comparison: 2 RUTF (total daily requirements) versus RUTF supplement, outcome: 2.3 Mortality.

Secondary outcomes

Weight gain

We did not pool results for RUTF as a supplement versus RUTF (total daily requirements) because of substantial heterogeneity ($\text{Chi}^2 = 4.26$; $\text{df} = 1$; P value = 0.04; $I^2 = 76.5\%$) (Analysis 2.4) (Manary 2004; Ndekha 2005). Both of these trials measured weight gain during the first four weeks of the intervention period. Manary 2004 found HIV-uninfected children in the supplement group gained less weight than children who received RUTF (MD -2.10 g/kg/day; 95% CI -3.08 to -1.12; $n = 158$). For HIV-infected children, we detected no difference in weight gain between the two groups (MD -0.10 g/kg/day; 95% CI -1.73 to 1.53; $n = 48$) (Ndekha 2005).

Time to recovery

HIV-uninfected children who received RUTF supplementary to their habitual diet recovered faster than those from the RUTF (total daily requirements) group (MD 10.0 days; 95% CI 0.87 to 19.13; $n = 116$) (Analysis 2.5) (Manary 2004). The HIV-infected children in the supplement group required a median of 115 days (interquartile range 59 to 195) to reach 100% weight for height while those in the RUTF group recovered within a median of 71 days (interquartile range 42 to 125) (WHO/National Center for Health Statistics (NCHS) standard) (P value not reported in the article) (Ndekha 2005).

Mid-upper arm circumference (MUAC) gain

We detected no difference in MUAC gain during the first four weeks of the intervention period between the two groups (MD -0.11 mm/day; 95% CI -0.22 to 0.01; $n = 173$) (Analysis 2.6) (Manary 2004; Ndekha 2005) and no significant heterogeneity was detected between the trials ($\text{Chi}^2 = 1.35$; $\text{df} = 1$; P value = 0.25; $I^2 = 26\%$). When separating results for HIV-infected and HIV-uninfected subgroups, children in the supplement group fared worse than children in the RUTF group in HIV-uninfected children (MD -0.15 mm/day; 95% CI -0.27 to -0.03; $n = 125$) (Manary 2004) while in HIV-infected children there was no difference detected (MD -0.03 mm/day; 95% CI -0.20 to 0.14; $n = 48$) (Ndekha 2005).

Weight for height z scores (WHZ)

HIV-uninfected children who recovered and were discharged from the trial were followed up for six months (Manary 2004). Results were obtained from the study author, which indicated that there was no difference in WHZ between children who received RUTF as a supplement and those who received RUTF (total daily requirements) (MD -0.10; 95% CI -0.56 to 0.36; $n = 73$). There were no baseline WHZ differences between the groups. Therefore, the differences in WHZ gain between the groups were not compared and would not have made a significant impact on the findings.

Adverse outcomes

Ndekha 2005 measured the “prevalence of diarrhoea” (days of diarrhoea divided by the “total days” during the first two weeks of the intervention period) in HIV-infected children. Study authors reported that children in the supplement group had diarrhoea on 38 out of the 432 days while children in the RUTF group had diarrhoea on 19 out of the 304 evaluation days. We were unsure about the meaning of “total days” as the figures did not correspond to the total number of days of each participant for each group. Since the corresponding numbers of participants were not reported, no treatment effect could be calculated.

Comparison 3: RUTF containing less milk powder versus standard RUTF

In a comparison of standard RUTF (25% milk powder) versus a formula of RUTF that contains less milk powder (10%), we found one individually randomised trial with 1874 HIV-uninfected children between 6 and 59 months of age in Malawi (Oakley 2010).

Primary outcomes

Recovery

Oakley 2010 defined recovery as having a WHZ greater than -2 without oedema within a maximum of eight weeks. We detected no difference in recovery between the two groups who received different formulations of RUTF (RR 0.97; 95% CI 0.93 to 1.01; $n = 1874$) (Analysis 3.1).

Relapse

Oakley 2010 defined relapse as the number of children who remained wasted plus the number of children who were referred to inpatient care. More children in the 10% milk RUTF group relapsed than children in the 25% milk RUTF group (RR 1.33; 95% CI 1.03 to 1.72; $n = 1874$) (Analysis 3.2).

Mortality

We found that the group that received the 10% milk RUTF had a similar number of deaths compared with the 25% milk RUTF group (RR 0.90; 95% CI 0.55 to 1.45; $n = 1874$) (Analysis 3.3) (Oakley 2010).

Secondary outcomes

Weight gain

Oakley 2010 measured weight gain during the intervention period. Children in the 10% milk RUTF group gained less weight than children in the 25% milk RUTF group (MD -0.50 g/kg/day; 95% CI -0.75 to -0.25; $n = 1874$) (Analysis 3.4).

Mid-upper arm circumference (MUAC) gain

Oakley 2010 measured MUAC. The time point was not reported. Children who received the 10% milk RUTF had less MUAC gain than children who received the 25% milk RUTF (MD -0.04 mm/day; 95% CI -0.06 to -0.02; n = 1874) (Analysis 3.5).

Weight for height z score (WHZ)

When comparing the end values between the two groups who received different RUTF formulations, we detected no difference in WHZ (MD 0.00; 95% CI -0.10 to 0.10; n = 1874) (Analysis 3.6) (Oakley 2010).

Weight for age z score (WAZ)

When comparing the end values between the 10% milk RUTF and 25% milk RUTF groups, we detected no difference in WAZ (MD -0.10; 95% CI -0.21 to 0.01; n = 1874) (Analysis 3.7) (Oakley 2010).

Height for age z score (HAZ)

When comparing the end values between the two groups who received different RUTF formulations, we detected no difference in HAZ (MD -0.10; 95% CI -0.24 to 0.04; n = 1874) (Analysis 3.8) (Oakley 2010).

Adverse outcomes

Oakley 2010 did not measure adverse outcomes.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Patient or population: children aged 6 months to 5 years with severe acute malnutrition Settings: home-based Intervention: RUTF supplement Comparison: RUTF (total daily requirements)						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	RUTF (total daily requirements)	RUTF supplement				
Recovery Different definitions ¹ Follow-up: during intervention period	830 per 1000	589 per 1000 (498 to 697)	RR 0.71 (0.6 to 0.84)	210 (2 studies)	⊕○○○ very low ^{2,3,4}	-
Relapse Admission to inpatient therapeutic care Follow-up: during intervention period	0 per 1000	0 per 1000 (0 to 0)	RR 8.95 (1.18 to 67.77)	210 (2 studies)	⊕○○○ very low ^{2,4,5,6}	-
Mortality Follow-up: during intervention period	68 per 1000	50 per 1000 (17 to 149)	RR 0.73 (0.25 to 2.18)	210 (2 studies)	⊕○○○ very low ^{2,4,6}	-
Weight gain: HIV-uninfected children (g/kg/day) Follow-up: first 4 weeks of intervention period	-	The mean weight gain: HIV-uninfected children in the intervention groups was 2.1 lower (3.08 to 1.12 lower)	-	158 (1 study)	⊕○○○ very low ^{7,8}	Weight gain in g/kg/day for a 6-kg child translates to a clinically important difference of MD 378 g/month (95% CI 201.6 to 554.4)

Weight gain: HIV-infected children (g/kg/day) Follow-up: first 4 weeks of intervention period	-	The mean weight gain: HIV-infected children in the intervention groups was 0.1 lower (1.73 lower to 1.53 higher)	-	48 (1 study)	⊕○○○ very low ^{8,9,10}	Weight in g/kg/day for a 6-kg child translates to a clinically important difference of either a loss of 311.4 g/month or a gain of 275.4 g/month
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HIV:** human immunodeficiency virus; **MD:** mean difference; **RR:** risk ratio; **RUTF:** ready-to-use therapeutic food.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ The 2 studies used different definitions for recovery. Manary 2004: reaching WHZ ≥ 0 ; Ndekha 100% weight for height.

² Downgraded by 2 for risk of bias: both studies had a high risk of selection bias and a high risk of attrition bias. In Manary 2004, the attrition was 26.0% and 10.1% in the RUTF supplement and RUTF (total daily requirements) groups, respectively; and in Ndekha 2005, the attrition was 28.6% and 10.0% in the 2 groups, respectively.

³ Not downgraded for inconsistency: 1 study was in HIV-uninfected children (Manary 2004) and 1 study was in HIV-infected children (Ndekha 2005). The effect estimate was similar in both studies.

⁴ Downgraded by 1 for indirectness: both studies were conducted in the same country (Malawi) and by a similar group of investigators. This limits the generalisability to other countries.

⁵ Not downgraded for inconsistency, but with only two studies with wide CIs, the meta-analysis is unlikely to detect heterogeneity.

⁶ Downgraded by 1 for imprecision: CIs are wide.

⁷ Downgraded by 2 for risk of bias: high risk of selection bias and high risk of attrition bias. Attrition was 26.0% in the RUTF supplement group and 10.1% in the RUTF (total daily requirements) group.

⁸ Downgraded by 1 for indirectness: only one small study, therefore, generalisability to other countries is not clear.

⁹ Downgraded by 1 for risk of bias: high risk of selection bias and high risk of attrition bias. Attrition was 10% and 28.6% in the RUTF (total daily requirements) and RUTF supplement groups, respectively.

¹⁰ Downgraded by 1 for imprecision: confidence interval includes both a clinically important gain or loss in weight.

Patient or population: children aged 6 months to 5 years with severe acute malnutrition Settings: home-based Intervention: RUTF containing less milk powder Comparison: standard RUTF						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard RUTF	RUTF containing less milk powder				
Recovery Having a WHZ > -2 without oedema Follow-up: maximum 8 weeks ¹	836 per 1000	811 per 1000 (777 to 844)	RR 0.97 (0.93 to 1.01)	1874 (1 study)	⊕⊕⊕○ moderate ²	-
Relapse Children who remained wasted plus children referred to inpatient care Follow-up: maximum 8 weeks ¹	98 per 1000	131 per 1000 (101 to 169)	RR 1.33 (1.03 to 1.72)	1874 (1 study)	⊕⊕○○ low ^{2,3}	-
Mortality Follow-up: maximum 8 weeks ¹	36 per 1000	32 per 1000 (20 to 52)	RR 0.90 (0.55 to 1.45)	1874 (1 study)	⊕○○○ very low ^{2,4}	-
Weight gain (g/kg/day) Follow-up: maximum 8 weeks ¹	-	The mean weight gain in the intervention groups was 0.5 lower (0.75 to 0.25 lower)	-	1874 (1 study)	⊕⊕○○ low ^{2,5}	Weight in g/kg/day for a 6-kg child translates to a clinically unimportant difference of a loss of MD 90 (95% CI 135 to 45) g/month

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **RUTF:** ready-to-use therapeutic food.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ The intervention period was up to 8 weeks, but outcome data for children who recovered, relapsed or died before 8 weeks was captured until the time the child was finished with the study.

² Downgraded by 1 for indirectness: only one study, therefore, generalisability is not assured.

³ Downgraded by 1 for imprecision: wide CI suggesting 3% to 72% more relapses with RUTF containing less milk powder.

⁴ Downgraded by 1 for imprecision: wide CI suggesting either a benefit or harm with RUTF containing less milk powder.

⁵ Downgraded by 1 for imprecision: wide CI suggesting 25% to 75% less weight gain with RUTF containing less milk powder.

DISCUSSION

Summary of main results

Our review aimed to assess the effects of home-based RUTF on relapse, mortality and weight gain in children with SAM. We found four eligible studies, of which three were quasi-randomised cluster trials that addressed three different comparisons. The total effective sample size was 2594 children. We found the risk of bias to be high for the three quasi-randomised trials, while the fourth trial had a low to moderate risk of bias. One of the studies included HIV-infected children, and all relevant meta-analyses were subgrouped according to HIV status. The number of studies and sample size per subgroup was too small to justify reporting the summarised results separately. We have displayed the most important findings in [Summary of findings for the main comparison](#), [Summary of findings 2](#) and [Summary of findings 3](#) and summarised our findings narratively below.

RUTF meeting total daily requirements versus standard diet (flour porridge)

When comparing RUTF versus standard diet (flour porridge) we found three quasi-randomised cluster trials ($n = 599$). RUTF may improve recovery slightly (RR 1.32; 95% CI 1.16 to 1.50; low-quality evidence), but we do not know whether RUTF improves relapse, mortality or weight gain (very low quality evidence).

RUTF supplement versus RUTF meeting total daily requirements

When comparing RUTF supplement versus RUTF that meets total daily nutritional requirements we found two quasi-randomised cluster trials ($n = 210$). For recovery, relapse, mortality and weight gain the quality of evidence was very low; therefore, the effects of RUTF are unknown.

RUTF containing less milk powder versus standard RUTF

When comparing a cheaper RUTF containing less milk powder (10%) versus standard RUTF (25% milk powder), we found one trial that randomised 1874 children. For recovery, there probably was little or no difference between the groups (RR 0.97; 95% CI 0.93 to 1.01; moderate-quality evidence). RUTF containing less milk powder may lead to slightly more children relapsing (RR 1.33; 95% CI 1.03 to 1.72; low-quality evidence) and to less weight gain (MD -0.5 g/kg/day; 95% CI -0.75 to -0.25; low-quality evidence) than standard RUTF. We do not know whether the cheaper RUTF improves mortality (very low quality evidence).

Overall completeness and applicability of evidence

In this review, we sought to evaluate the best evidence regarding the efficacy and safety of RUTF as home-based treatment. Should RUTF be found to be more efficacious than the standard diet, then, from a health systems perspective, it would be important to know whether the cheaper RUTF regimen (RUTF as a supplement) and formulation (reduced milk powder content) could achieve similar or better health outcomes. From a nutritional perspective, it is important that the children's carers sustain and improve cultural-specific dietary habits instead of relying solely on provided medical nutritional therapy. The abovementioned issues informed the three comparisons investigated in this systematic review. Although a number of trials have been conducted with RUTF (for example, see the [Characteristics of excluded studies](#) table), a limited number of *randomised controlled* trials investigated the comparisons we identified as being most important for SAM children.

The studies included in this review have a number of limitations in respect of external validity. For example, each of the studies assessed a wide age range and did not allow for exploration of possible differences in effect between younger and older children. Furthermore, comorbidities such as HIV, which may have considerable impacts on growth and immunity, are not sufficiently addressed in the current body of evidence. There is a lack of information on participants' total daily energy intake per group as well as the likelihood of sharing RUTF and standard diet with the family and whether something was done to prevent differential sharing. In addition, the issue of allergies was not sufficiently addressed. In all four included studies, children were exposed to peanuts and soy, which are both known allergens. However, no study tested for soy allergies, and only two studies tested for peanut allergies ([Manary 2004](#); [Ndekha 2005](#)).

No included study followed up children for more than six months and, therefore, we could not evaluate potential long-term growth and developmental differences. Specifically, no study assessed cognitive function and development, which is important for future school performance. Furthermore, studies employed different definitions for outcomes such as recovery (different reference standards and cut-off points) and anthropometrical measurements (assessed at different time points). One of the theoretical benefits of RUTF is a low water availability (thus less likely to become contaminated with microorganisms), which should lead to fewer episodes of diarrhoea. However, diarrhoea was not a primary outcome in any of the included studies, despite the fact that diarrhoea is one of the biggest causes of mortality in young children. More emphasis must be placed on this in future RUTF research. Overall, we consider that the current body of evidence for the three comparisons addressed in this review lacks important information to allow evaluation of applicability in different types of children and settings.

Quality of the evidence

The reporting of trials included in this review was generally poor,

thus necessitating contact with the trial authors. We are grateful to the authors for providing data requested for our analysis. With our risk of bias assessment, we identified the following to be of high concern: selection bias (as three of the four included studies were quasi-randomised trials), attrition bias and reporting bias. The few included studies were not suitable for sensitivity analyses. As shown by our GRADE assessments ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#)), the quality of evidence varied between moderate and very low, which means that future research is likely to impact on the findings. Therefore, our confidence in the findings is limited.

One key methodological limitation of the included studies is the lack of a definition for SAM. Only [Oakley 2010](#) explicitly defined SAM. Baseline characteristics were taken upon enrolment (after the stabilisation period) while diagnosis of SAM was made before stabilisation. Therefore, improvement in nutritional status during the stabilisation period is not reflected in the baseline characteristics reported in the included articles, which raises concern about whether the children were severely malnourished at the start of the trials.

Potential biases in the review process

It is unlikely that we have missed any relevant trials since, apart from our electronic search without any language restriction, we also contacted the corresponding authors of the included studies (and some of the excluded studies) as well as professionals working in the field.

We were unable to assess the likelihood of publication bias formally due to the small number of studies per comparison.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review that specifically compared home-based RUTF with standard diet for the treatment of SAM children. However, we are aware of another review where the “efficacy and safety of home-based management of SAM using ‘therapeutic nutrition products’ or ready to use therapeutic foods and efficacy of these products in comparison with F100 and home-based diet” were assessed ([Gera 2010](#)). We evaluated the methodological quality of [Gera 2010](#) with the validated AMSTAR tool ([Shea 2007](#)), and presented our findings in [Table 13](#). Although [Gera 2010](#) was published as a systematic review, the methods followed did not meet all of the requirements.

[Gera 2010](#) included two reviews, seven “controlled trials”, seven cohort studies and two consensus statements. The outcomes assessed were recovery rate (as defined by the study authors), weight gain (g/kg/day), relapse, mortality and morbidities (for example, diarrhoea, malaria and respiratory infections). Of the seven “controlled trials”, we have included two in our review ([Manary 2004](#); [Ciliberto 2005](#)). We did not include the remaining five trials be-

cause one was facility-based ([Diop 2003](#)), three did not have an eligible control group ([Diop 2004](#); [Sandige 2004](#); [Gabouland 2007](#)), and one trial included Spirulina® and not RUTF ([Simpore 2006](#)). [Gera 2010](#) did not perform a meta-analysis of trials on any of the comparisons that we evaluated in our review but pooled four cohort studies that assessed the effect of home-based RUTF on weight gain in SAM children and found a “mean weight gain” (type of effect size not specified) of 3.2 g/kg/day (95% CI 3.06 to 3.34; $I^2 = 89.8\%$) (software and effects model not reported). In our review, we also found that children who received RUTF as opposed to standard diet gained more weight. However, our MD is smaller (MD 1.47 g/kg/day; 95% CI 0.49 to 2.45; random-effects analysis, heterogeneity $\text{Chi}^2 = 2.92$; $I^2 = 32\%$; [Analysis 1.4](#)). [Ashworth 2006](#) and [Bhutta 2008](#) evaluated the efficacy of interventions for malnutrition in young children, which included RUTF. While the authors did not comment on the effectiveness of RUTF versus standard diet, they did report that RUTF could be used in home-based settings.

Another Cochrane systematic review that will evaluate nutritional therapy for malnutrition is underway. [Lazzerini 2012](#) is evaluating the “safety and effectiveness of different types of foods for children with moderate acute malnutrition (MAM) in low- and middle-income countries”. RUTF will be included in this review, and when completed, will complement our systematic review relating to SAM children.

AUTHORS' CONCLUSIONS

Implications for practice

Given the limited evidence base currently available, it was not possible to reach definitive conclusions regarding differences in clinical outcomes in children with SAM who were given home-based RUTF compared to the standard diet, or who were treated with RUTF in different daily amounts or formulations.

Implications for research

Well-designed, adequately powered pragmatic RCTs (reported according to the CONSORT (CONsolidated Standards of Reporting Trials) guidelines) of RUTF are needed. Specifically, the focus needs to be on recovery, relapse and mortality, but also on adverse effects such as diarrhoea and allergic reactions, as these are the outcomes important to patients. In addition, cost implications should be reported in future studies to enable a cost-effectiveness analysis.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ciliberto 2005

Methods	<p>Study design: stepped wedge design treated as quasi-randomised cluster trial</p> <p>Study duration: stepwise enrolment to a 8-week treatment period (or until reaching WHZ > 0); those who reached WHZ > -2 were followed up 6 months after end of intervention period</p> <p>Recruitment date: December 2002 to June 2003</p>
Participants	<p>Children: MAM and SAM, but only data for SAM children are used in this review. Definitions for MAM and SAM were not provided</p> <p>Total number randomised: 645 SAM children (532 in the experimental and 113 in the control group); effective sample size 352 (290 in the experimental and 62 in the control group)</p> <p>Country and setting: southern Malawi; outpatients to NRUs</p> <p>Inclusion criteria: aged 10-60 months; attending 1 of 7 NRUs as in- or outpatient; wasting (WHZ < -2), mild oedema (< 0.5 cm pitting oedema on the dorsum of the foot), or both, and a good appetite</p> <p>Exclusion criteria: severe oedema (> 0.5 cm pitting oedema on the dorsum of the foot); systemic infection; anorexia</p> <p>Baseline characteristics of experimental group (including MAM children): 526/992 males; mean age 23 SD 10 months; oedema 434/992; mean weight 7.7 SD 1.7 kg; mean length 74.8 SD 6.6 cm; WAZ -3.5 SD 1.0; HAZ -3.0 SD 1.5; WHZ -2.2 SD 0.8; mean MUAC 11.6 SD 1.4 cm; children still breastfeeding 505/992; mean age when breastfeeding stopped 21 SD 7 months; 347/992 were hospitalised prior to the study (mean 11 SD 9 days)</p> <p>Baseline characteristics of control group (including MAM children): 98/186 males; mean age 24 SD 12 months; oedema 86/186; mean weight 7.6 SD 1.9 kg; mean length 75.0 SD 7.6 cm; WAZ -3.7 SD 1.0; HAZ -3.2 SD 1.6; WHZ -2.5 SD 0.9; mean MUAC 11.6 SD 1.5 cm; children still breastfeeding 72/186; mean age when breastfeeding stopped 21 SD 8 months; 186/186 were hospitalised prior to the study (mean 22 SD 14 days)</p> <p>Stabilised before start of study: yes, the "very ill" received F75 containing 75 kCal/100 mL and 0.9 g protein/100 mL; parenteral antibiotics</p>
Interventions	<p>RUTF: locally produced by the study team and Tambala Foods (Blantyre, Malawi); ingredients were 25% peanut butter, 28% sugar, 30% full-fat milk; 15% vegetable oil; 1.4% imported micronutrients (Nutraset); 260 g daily portion provided 175 kCal/kg/day and 5.3 g/kg/day protein</p> <p>Standard diet: F100 when in the NRU and maize/soy blended flour supplemented with micronutrients at home; blended flour (80% maize, 20% soy) prepared by carer and to be consumed 7 times/day; the family each participant received 50 kg of flour</p> <p>Concomitant treatment: not reported</p>
Outcomes	<p>Recovery (the attainment of a WHZ > -2 while remaining free of oedema)</p> <p>Relapse during intervention period (recurrence of oedema or systematic infection requiring readmission to NRU)</p> <p>Relapse after the study (WHZ < -2 or oedema 6 months after recovery)</p>

	Mortality (all reported child deaths were considered to be a consequence of malnutrition) Weight gain (g/kg/day during the first 4 weeks of the intervention period) MUAC gain (mm/day during the first 4 weeks of the intervention period) Height gain (length/height in mm/day over 8 weeks of treatment) Diarrhoea (days with diarrhoea as reported by carer)
Notes	Ethics approval: College of Medicine Research and Ethics Committee of the University of Malawi; Human Studies Committee of Washington University in St Louis Informed consent: obtained; not reported whether it was orally or in writing Financial contributors: Doris Duke Clinical Scholars Programme; St Louis Children's Hospital Foundation; World Food Programme; Valid International; US Agency for International Development Reference standard for anthropometrical data: NCHS reference population (EPI 2002 version 1.1.2, Centers for Disease Control and Prevention, Atlanta, USA) Quality of anthropometrical measurements: unclear as no relevant information was reported Tested for peanut allergies: no

<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"...systematic allocation with a stepped wedge design..."
Allocation concealment (selection bias)	High risk	Quasi-randomised study, therefore, prediction of next allocation possible
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Children across groups received the same contact time with study personnel, thus low risk for performance bias. No blinding, thus unclear risk for detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up not differential and small: 98/992 (9.9%) from the experimental group and 15/186 (8.1%) from the control group dropped out of the study
Selective reporting (reporting bias)	Unclear risk	Protocol not available; primary and secondary outcome prespecified in the Methods section and addressed in the Results section
Other bias	Unclear risk	At baseline, the standard diet group had worse WHZ and longer prior hospital stay

Methods	<p>Study design: quasi-randomised trial (randomising clusters that were the day of the child's discharge in the month); parallel group design</p> <p>Study duration: maximum of 16 weeks' intervention period or until children reached WHZ > 0, relapsed or died; recovered children were followed up 6 months after being discharged from study</p> <p>Recruitment date: 25 January to 15 October 2001</p>
Participants	<p>Children: SAM children, where a definition for SAM was not provided</p> <p>Total number randomised: 282 (RUTF (total daily requirements) n = 69; RUTF supplement n = 96; maize/soy flour n = 117); effective sample size 275 (67 in the RUTF (total daily requirements), 94 in the RUTF supplement, and 114 in the maize/soy flour group)</p> <p>Country and setting: Malawi; outpatients from the Queen Elizabeth Central Hospital in Blantyre</p> <p>Inclusion criteria: aged > 12 months; discharged from the study hospital</p> <p>Exclusion criteria: HIV-positive as determined by ELISA where positive tests were confirmed with "a second test"</p> <p>Baseline characteristics of RUTF group: 42/69 males; mean age 29 SD 18 months; oedema during hospitalisation 56/69; mean length of hospital stay 13 SD 9 days; WAZ -3.4 SD 1.3; HAZ -3.5 SD 2.0; WHZ -1.8 SD 0.8; mean MUAC 12.0 SD 1.7 cm; mean age weaned 19 SD 7 months</p> <p>Baseline characteristics of RUTF supplement group: 56/96 males; mean age 28 SD 14 months; oedema during hospitalisation 77/96; mean length of hospital stay 14 SD 8 days; WAZ -3.6 SD 1.1; HAZ -3.7 SD 1.6; WHZ -2.0 SD 0.9; mean MUAC 11.9 SD 1.5 cm; mean age weaned 20 SD 7 months</p> <p>Baseline characteristics of maize/soy flour group: 69/117 males; mean age 29 SD 13 months; oedema during hospitalisation 98/117; mean length of hospital stay 11 SD 5 days; WAZ -3.4 SD 1.0; HAZ -3.6 SD 1.3; WHZ -1.9 SD 1.0; mean MUAC 11.9 SD 1.8 cm; mean age weaned 19 SD 7 months</p> <p>Stabilised (e.g. with F-75) before start of study: treated for acute bacterial infection; received "feedings" providing 420 kJ/kg/day and 1.2 g protein/kg/day; "supportive care for acute metabolic complications"</p>
Interventions	<p>RUTF (total daily requirements): industrially prepared (Nutraset, Malaunay, France); contained peanut butter, milk powder, oil, sugar and micronutrients; providing 733 kJ/kg/day; received 276 g/day</p> <p>RUTF supplement: industrially prepared (Nutraset, Malaunay, France); contained peanut butter, milk powder, oil, sugar and micronutrients; providing 2090 kJ/day; received 92 g/day</p> <p>Maize/soy flour: assumed to be locally produced; comprised 80% maize and 20% soy flour; prepared by carer as "nzima"; providing 4 kJ/g; received 2400 g/day (enough for whole family)</p> <p>Concomitant treatment: children in the RUTF and maize/soy groups received enough food to cover daily energy requirements but other food intake was not monitored; children in the RUTF supplement group were advised to continue with their "habitual diet" in addition to the received RUTF</p>
Outcomes	<p>Recovery (WHZ $\geq$ 0; "WHO's reference population")</p> <p>Relapse (admission to inpatient therapeutic care during the study period)</p> <p>Time to recovery</p>

	Weight gain (g/kg/day during the first 4 weeks of the intervention period) MUAC gain (mm/day during the first 4 weeks of the intervention period) WHZ (6 months after recovery; "WHO's reference population") Height gain (length was converted to height by subtracting 0.5 cm for children > 84.9 cm; mm/day during the first 4 weeks of the intervention period) Diarrhoea (days with diarrhoea as reported by carers)
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Notes	Ethics approval: College of Medicine Research Committee of the University of Malawi; Human Studies Committee of Washington University in St Louis Informed consent: obtained; not reported whether it was orally or in writing Financial contributors: Allen Foundation; Craig and Benith MacPherson; RUTF donated by Nutriset (Malaunay, France) Reference standard for anthropometrical data: WHO's reference population (Epi 2000 version 1.1.2, Centers for Disease Control and Prevention, Atlanta, USA) Quality of anthropometrical measurements: length was converted to height by subtracting 0.5 cm for children > 84.9 cm; for other measurements no relevant information was reported Tested for peanut allergy: yes; no child found to be allergic
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<i>Risk of bias</i>		<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"...systematic allocation determined by the day of the child's discharge in the month"
Allocation concealment (selection bias)	High risk	Quasi-randomised study, therefore, prediction of next allocation possible
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Children across groups received the same contact time with study personnel, thus low risk for performance bias. Blinding not reported, thus unclear risk for detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential loss to follow-up: 7/69 (10.1%), 25/96 (26.0%) and 15/117 (12.8%) children dropped out of the RUTF, RUTF supplement and maize/soy groups, respectively
Selective reporting (reporting bias)	Unclear risk	Protocol not available, but primary and secondary outcomes were stated in the Methods section and addressed in the Results section
Other bias	Unclear risk	Balanced baseline characteristics for those randomised per group. Nutriset donated the experimental food. Families with a child in the maize/soy flour group received

		enough to feed them all, but it is possible that children who received RUTF or RUTF supplement shared it with siblings or other family members
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Ndekha 2005

Methods	<p>Study design: quasi-randomised trial (randomising clusters that were the week of the child's discharge in the month); parallel group design</p> <p>Study duration: until children reached 100% WHZ, relapsed or died; recovered children were followed up 6 months after being discharged from study</p> <p>Recruitment date: January to September 2001</p>
Participants	<p>Children: SAM, where a definition for SAM was not provided</p> <p>Total number randomised: 93 (RUTF (total daily requirements) n = 20; RUTF supplement n = 28; maize/soy flour n = 45); effective sample size 93 (20 in the RUTF (total daily requirements), 28 in the RUTF supplement, and 45 in the maize/soy flour group)</p> <p>Country and setting: Malawi; outpatients from the Queen Elizabeth Central Hospital in Blantyre</p> <p>Inclusion criteria: HIV-infected (ELISA; positive test results were confirmed by Western blot); 12-60 months old; discharged from the study hospital; "severely malnourished" (not defined by authors)</p> <p>Exclusion criteria: not reported</p> <p>Baseline characteristics of RUTF group: 11/20 males; mean age 25 SD 10 months; oedema during hospitalisation 13/20; mean length of hospital stay 13 SD 12 days; WAZ -3.6 SD 0.9; HAZ -3.6 SD 1.0; WHZ -2.0 SD 1.1; MUAC 11.2 SD 1.7 cm</p> <p>Baseline characteristics of RUTF supplement group: 14/28 males; mean age 27 SD 16 months; oedema during hospitalisation 11/28; mean length of hospital stay 11 SD 6 days; WAZ -4.0 SD 1.0; HAZ -3.4 SD 1.5; WHZ -2.8 SD 0.9; MUAC 10.6 SD 1.4 cm</p> <p>Baseline characteristics of maize/soy flour group: 23/45 males; mean age 24 SD 9 months; oedema during hospitalisation 19/45; mean length of hospital stay 14 SD 7 days; WAZ -3.7 SD 0.9; HAZ -4.0 SD 1.3; WHZ -1.8 SD 0.8; MUAC 11.3 SD 1.5 cm</p> <p>Stabilised (e.g. with F-75) before start of study: treated for acute bacterial infection; received "feedings" providing 420 kJ/kg/day and 1.2 g protein/kg/day; "supportive care for acute metabolic complications"</p>
Interventions	<p>RUTF (total daily requirements): industrially prepared (Nutraset, Malaunay, France); contained peanut butter, milk powder, oil, sugar and micronutrients; providing 733 kJ/kg/day; received 276 g/day</p> <p>RUTF supplement: industrially prepared (Nutraset, Malaunay, France); contained peanut butter, milk powder, oil, sugar and micronutrients; provided 2090 kJ/day; received 92 g/day</p> <p>Maize/soy flour: 80% maize and 20% soy flour blend; prepared by carer as "nzima"; provided 4 kJ/g; received 2400 g/day (enough for whole family)</p> <p>Concomitant treatment: children in the RUTF and maize/soy groups received enough food to cover daily nutritional requirements but other food intake was not monitored;</p>

	children in the RUTF supplement group were advised to continue with their “habitual diet” in addition to the received RUTF
Outcomes	Recovery (reaching 100% weight for height; WHO reference population) Relapse (admission to inpatient therapeutic care) Mortality Time to recovery Weight gain (g/kg/day during the first 4 weeks of the intervention period) MUAC gain (mm/day during the first 4 weeks of the intervention period) Diarrhoea (days of diarrhoea as reported by cares divided by the total days during the first 2 weeks of the intervention period)
Notes	Ethics approval: College of Medicine Research Committee of the University of Malawi; Human Studies Committee of Washington University in St Louis Informed consent: obtained; not reported whether orally or in writing Financial contributors: Allen Foundation; Craig and Benith MacPherson; RUTF donated by Nutriset (Malaunay, France) Reference standard for anthropometrical data: WHO’s reference population (Epi 2000 version 1.1.2, Centers for Disease Control and Prevention, Atlanta, USA) Quality of anthropometrical measurements: unclear as no relevant information was reported Tested for peanut allergy: probably because in Manary 2004 it is reported that “no evidence of peanut allergy was found in this whole population”

*Risk of bias**Risk of bias*

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	High risk	“...systematically allocated...based on their week of discharge from the hospital”
Allocation concealment (selection bias)	High risk	Quasi-randomised study, therefore, prediction of next allocation possible
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Children across groups received the same contact time with study personnel, thus low risk for performance bias. Blinding not reported, thus unclear risk for detection bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential loss to follow-up: 2/20 (10%) , 8/28 (28.6%) and 7/45 (15.6%) children dropped out of the RUTF, RUTF supplement and maize/soy groups, respectively
Selective reporting (reporting bias)	High risk	Protocol not available; primary and secondary outcomes were prespecified in the Methods section and addressed in the Results section. However, results for “time to recovery” were reported although not pre-

		specified in the Methods section as an outcome
Other bias	Unclear risk	At baseline, children in RUTF supplement group were more wasted. Nutriset donated the experimental food. Families with a child in the maize/soy flour group received enough to feed them all, but it is possible that children who received RUTF or RUTF supplement had to share it with siblings or other family members

Oakley 2010

Methods	<p>Study design: individually randomised controlled trial; parallel group design</p> <p>Study duration: children were discharged upon recovery, but were given a maximum of 8 weeks</p> <p>Recruitment date: July 2008 to April 2009</p>
Participants	<p>Children: SAM, where the following definition for SAM was provided: "WHZ < -3 and/or having bipedal pitting oedema"</p> <p>Total number randomised: 1874 (929 received RUTF containing less milk powder (experiment) and 945 received standard RUTF (control))</p> <p>Country and setting: rural, southern Malawi; outpatients</p> <p>Inclusion criteria: SAM children 6-59 months of age, defined as WHZ < -3 with or without oedema; good appetite, defined as being able to consume 30 g of RUTF upon presentation</p> <p>Exclusion criteria: chronic illness, including HIV; having participated in a treatment programme for SAM within the past 3 months</p> <p>Baseline characteristics of RUTF containing less milk powder group: 388/929 males; mean age 19.5 SD 9.7 months; oedema 721/929; WAZ -3.1 SD 1.2; HAZ -3.0 SD 1.5; WHZ -2.0 SD 1.2; MUAC 12.2 SD 1.3 cm; still being breastfed 539/925; diarrhoea on admission 387/929</p> <p>Baseline characteristics of standard RUTF group: 432/945 males; mean age 19.2 SD 9.9 months; oedema 737/945; WAZ -3.1 SD 1.2; HAZ -3.0 SD 1.5; WHZ -2.1 SD 1.2; MUAC 12.1 SD 1.3 cm; still being breastfed 555/938; diarrhoea on admission 419/945</p> <p>Stabilised (e.g. with F-75) before start of study: not reported</p>
Interventions	<p>RUTF containing less milk powder: locally produced RUTF containing 10% milk powder, 15% replaced with unprocessed soy flour; also included added micronutrients; provided 2000 kJ/100 g, protein 15 g/100 g, fat 40 g/100 g; packaged in 245 g plastic jars; received 733 kJ/kg/day</p> <p>Standard RUTF: locally produced RUTF containing 25% milk powder; also included added micronutrients; provided 2000 kJ/100 g, protein 15 g/100 g, fat 40 g/100 g; packaged in 245 g plastic jars; received 733 kJ/kg/day</p> <p>Concomitant treatment: not reported</p>

Outcomes	Recovery (WHZ > -2 without oedema) Relapse (remained wasted; referred for inpatient treatment) Mortality Weight gain (g/kg/day calculated over the duration of therapy) Height gain (mm/day, time point not reported) MUAC gain (mm/day, time point not reported) WAZ upon completion of study HAZ upon completion of study WHZ upon completion of study
Notes	Ethics approval: College of Medicine Research and Ethics Committee of the University of Malawi; Human Studies Committee of Washington University School of Medicine, USA Informed consent: oral and written from carers Financial contributors: Hickey Family Foundation; Academy for Educational Development; NIH grant T32 HD049338 Reference standard for anthropometrical data: "WHO 2006 standards" Quality of anthropometrical measurements: performed by trained, senior study staff; weight was measured with an electronic scale (SECA model 334) which was calibrated weekly to have a precision of 5 g; height (SECA model 412, precision 1 mm) and length (SECA model 210, precision 0.25 cm) were measured in triplicate and the mean value was used; MUAC was measured with a standard UNICEF insertion tape (precision 2 mm) Tested for peanut allergy: not reported

<i>Risk of bias</i>			<i>Risk of bias</i>
Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Low risk	"Children were randomly assigned with equal probability to either 25% milk RUTF or 10% milk RUTE.. Randomization was blocked for the entire study..."	
Allocation concealment (selection bias)	Low risk	"To allocate children to a food group, caretakers chose a sealed envelope that contained 1 of 6 letters: 3 of these letter corresponded to the 25% milk formulation and 3 to the 10% milk formulation"	
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Children across groups received the same contact time with study personnel, thus low risk for performance bias. "Caretakers, field workers and investigators assessing the children remained unaware of what type of food each child received for the duration of the study." However, what was done to secure blinding was not reported.	

		It is not clear from the article whether the two RUTF products looked, tasted and were packaged identically. Therefore, unclear risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up not differential and small: 23/929 (2.5%) from the RUTF containing less milk powder group and 28/945 (3%) from the standard RUTF group were loss to follow-up
Selective reporting (reporting bias)	High risk	Protocol available (ISRCTN54186063). Number of days of fever, cough and diarrhoea were prespecified in the protocol and, in the article, it was described that data for this outcome were collected. However, no results were reported
Other bias	Low risk	Balanced baseline characteristics for all randomised children. Industry was not involved in the study

All 4 studies were conducted by a similar group of investigators (i.e. same contact author and many of the co-authors overlapped). ELISA: enzyme-linked immunoabsorbent assay; HAZ: height for age z score; HIV: human immunodeficiency virus; kCal: kilocalories; kJ: kilojoules; MAM: moderate acute malnutrition; MUAC: mid-upper arm circumference; NCHS: National Center for Health Statistics; NRU: nutrition rehabilitation unit; SAM: severe acute malnutrition; SD: standard deviation; RUTF: ready-to-use therapeutic food; WAZ: weight for age z score; WHO: World Health Organization; WHZ: weight for height z score.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Amthor 2009	Not an RCT or quasi-randomised trial
Briend 1999	Not an RCT or quasi-randomised trial
Diop 2003	Facility-based RUTF
Diop 2004	Comparison not eligible as locally, non-commercially produced RUTF was compared to commercially produced RUTF
Dube 2009	Outcome not applicable (an acceptability trial)
Greco 2006	Not an RCT or quasi-randomised trial

(Continued)

Kuusipalo 2006	Treatment not RUTF
Lagrone 2010	Not an RCT or quasi-randomised trial
LaGrone 2012	Treatment not RUTF
Linneman 2007	Not an RCT or quasi-randomised trial
Lopriore 2004	Treatment not RUTF
Maleta 2004	Children not severely malnourished
Mamidi 2011	Not an RCT or quasi-randomised trial
Matilsky 2009	Treatment not RUTF
Nackers 2010	Children not severely malnourished
Navarro-Colorado 2005	Facility-based RUTF
Patel 2005	Prevention study
Phuka 2008	Treatment not RUTF
Sandige 2004	Comparison not eligible as locally, non-commercially produced RUTF was compared to commercially produced RUTF
Singh 2010	Children not severely malnourished
Thakwalakwa 2010	Treatment not RUTF
Van Hoan 2009	Treatment not RUTF

RCT: randomised controlled trial; RUTF: ready-to-use therapeutic food.

Characteristics of ongoing studies *[ordered by study ID]*

[CTRI/11/12/002259](#)

Trial name or title	Effectiveness of ready-to-use therapeutic food (RUTF) in community based management of uncomplicated severe acute malnutrition (SAM) in an urban resettlement area in Chandigarh: a randomized controlled trial
Methods	Randomised clinical trial; parallel group design

Participants	Inclusion criteria: children with uncomplicated SAM (WHZ < -3 SD or MUAC < 115 mm) with good appetite, alert and clinically well; living in the area for at least 6 months Exclusion criteria: complicated SAM children, meaning having 1 or more of symptoms such as anorexia, not alert, high fever (104 °F (40 °C)), severe pallor, severe hydration, lower respiratory tract infection, bipedal oedema, visible severe wasting
Interventions	Arm 1: RUTF in addition to standard management for a maximum of 12 weeks Arm 2: standard management
Outcomes	Primary outcome: <ul style="list-style-type: none"> proportion of children gaining 15% of the baseline weight for height (time point: 4-12 weeks)
Starting date	April 2004
Contact information	Name: Hemant Deepak Shewade, Chandigarh, India Email: hemantjipmer@gmail.com Name: Binor Kumar Patro, Chandigarh, India Email: patrobinod@gmail.com Name: Bhavneet Bharti Email: bhavneetb@yahoo.com
Notes	Location: India Sponsors: IAPSM Ford Foundation Epidemiological grant, New Delhi, India

CTRI/2012/10/003054

Trial name or title	A study on effects of three feeding regimens in promoting recovery in children with uncomplicated severe acute malnutrition
Methods	Randomised clinical trial; parallel group design
Participants	Inclusion criteria: children with SAM; WHZ < -3 SD of WHO standard or oedema of both feet Exclusion criteria: complicated SAM requiring hospitalisation; known allergy to animal milk or peanuts; likely to leave the study area permanently in the next 8 weeks
Interventions	Arm 1: RUTF produced commercially by Indian company Arm 2: RUTF produced non-commercially by study team Arm 3: high energy and micronutrient rich foods prepared by carers at home using ingredients provided to them
Outcomes	Primary outcome: <ul style="list-style-type: none"> recovery by 8 weeks defined as WHZ $\geq$ -2 SD and no oedema on feet Secondary outcomes (time frame enrolment to 8 weeks): <ul style="list-style-type: none"> cost of interventions feedback from families and healthcare professionals about the interventions: perceptions and feasibility of use mortality and hospitalisation proportion of children with diarrhoea

	<ul style="list-style-type: none"> • proportion of children with WHZ $\geq$ -2 SD and no oedema on feet • rate of weight gain (g/kg/day) • time to recovery
Starting date	October 2012
Contact information	Name: Nita Bhandari from New Delhi, India Email: chrd@sas.org.in
Notes	Location: India Sponsors: Bill and Melinda Gates Foundation, USA

ISRCTN62376241

Trial name or title	Acceptability, effectiveness and cost-effectiveness of soya maize sorghum-based ready-to-use therapeutic food in treating severe acute malnutrition in children under five in Lusaka, Zambia
Methods	Cluster-randomised clinical trial
Participants	<p>Inclusion criteria: boys and girls with SAM aged 6-59 months; MUAC < 110 mm or oedema present; admitted into the Outpatient Therapeutic Programme at the health centre; good appetite; no serious medical complication</p> <p>Exclusion criteria: children with SAM with no appetite or severe medical complications, or both, or with marasmic kwashiorkor, will be first stabilised in the University Teaching Hospital after which they will be enrolled in the study</p>
Interventions	<p>Arm 1: "soya, maize and sorghum-based RUTF"; 200 kCal/kg/day</p> <p>Arm 2: peanut-based RUTF; 200 kCal/kg/day</p> <p>Both groups will receive the food until recovery or exit, or both, from the programme (maximum stay is 17 weeks)</p>
Outcomes	<p>Primary outcome:</p> <ul style="list-style-type: none"> • recovery rate: data will be measured routinely and analysed monthly, with final analysis at the end of the study period <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • defaulter rate: data will be measured routinely and analysed monthly, with final analysis at the end of the study period • mean weight gain from baseline (or in oedematous children, from time of loss of oedema) until exit from the programme: weight gain will be measured for each individual child and a mean taken at the end for those who successfully complete the treatment • morbidity (diarrhoea, vomiting, fever, cough): incidence of morbidity will be compared weekly between the 2 groups, as well as at the end of the study period • Hospital referral: the number of children referred; outcome for referral will be measured and compared at the end of the study • Mortality: collected and analysed routinely; final analysis will be made at the end of the study as well as a comparison between the 2 arms • Length gain: height will be measured at admission, week 4, week 8 and at discharge

Starting date	June 2008
Contact information	Name: Abel Hailu Irena from Valid International, Lusaka, Zambia Email: abel@validinternational.org
Notes	Location: Zambia Sponsors: Valid Nutrition, UK; Irish Aid, Department of Foreign Affairs, Dublin, Ireland

NCT00131417

Trial name or title	Comparison of the efficacy of a ready-to-use therapeutic food with a milk-based diet in the rehabilitation of severely malnourished Ugandan children
Methods	Randomised clinical trial; parallel group design
Participants	Inclusion criteria: boys and girls aged 6-59 months with severe malnutrition (weight for height < 70% of median NCHS/WHO reference values); carer's informed consent for the study and HIV testing; children who have completed initial phase of management of severe malnutrition (without oedema, diarrhoea, vomiting) with normal temperature and gaining weight > 5 g/kg/day Exclusion criteria: serious medical conditions (e.g. severe pneumonia, cerebral palsy); persistent diarrhoea
Interventions	Arm 1: semi-solid RUTF; 545 kCal/100 g divided into 5 meals daily Arm 2: high-energy milk, which is reconstituted cows' milk with a nutritional composition similar to F100, which provides 100 kCal/100 mL
Outcomes	Primary outcomes: <ul style="list-style-type: none"> • mean weight gain (g/kg/day) • time in days taken to attain 85% weight for height (assumed to be 85% of the NCHS/WHO reference values) Secondary outcomes: <ul style="list-style-type: none"> • mortality • adverse effects
Starting date	October 2004
Contact information	Name: Harriet Nambuya, Makerere University, Uganda
Notes	Location: Uganda Sponsors and collaborators: Makerere University, Kampala, Uganda; Norwegian Programme for Development, Research and Education (NUFU)

NCT00941434

Trial name or title	Community based management of malnutrition. A proposal for Pakistan Initiative for Mothers and Newborns
Methods	“Step wedge randomised trial”
Participants	Inclusion criteria: boys or girls aged 6 months to 3 years with moderate to severe malnutrition; carer informed consent Exclusion criteria: chronic debilitating illness; reside outside study areas
Interventions	Arm 1: RUTF Arm 2: unclear
Outcomes	Primary outcome: <ul style="list-style-type: none"> improved growth parameters WAZ (time frame: 1 year) Secondary outcome: <ul style="list-style-type: none"> reduction in malnutrition-related morbidity and mortality patterns in early childhood (time frame: 1 year)
Starting date	July 2009
Contact information	Name: Zulfiqar A Bhutta, Aga Khan University, Pakistan
Notes	Location: Dadu, Sindh, Pakistan Sponsors and collaborators: Aga Khan University, Pakistan; John Snow Inc.; Pakistan Ministry of Health

NCT01144806

Trial name or title	Evaluation of energy expenditure, body composition and recovery rates in children with severe acute malnutrition (SAM) receiving community-based nutritional rehabilitation therapy
Methods	Randomised clinical trial
Participants	Inclusion criteria: girls and boys aged 6 months to 3 years; reside in study area Exclusion criteria: children with congenital malformations; chronic debilitating illnesses; refusal by parents to enrol in the study
Interventions	Arm 1: RUTF supplement, Plumpy'nut® Arm 2: nutrition education to carers using the principles of infant and young child feeding (IYCF) and dietary diversification
Outcomes	Primary outcome: <ul style="list-style-type: none"> body composition (time frame: 12 weeks)
Starting date	June 2010
Contact information	Name: Zulfiqar A Bhutta, Aga Khan University, Pakistan
Notes	Location: Pakistan Sponsors and collaborators: Aga Khan University, Pakistan; International Atomic Energy Agency

NCT01634009

Trial name or title	Efficacy of ready to use therapeutic food using soy protein isolate in under-5 children with severe acute malnutrition in Bangladesh
Methods	Randomised clinical trial, parallel group design
Participants	Inclusion criteria: boys and girls with SAM (WHZ < -3 SD of WHO standard) aged 6 months and 5 years; completed stabilisation; clinically well; no oedema and with appetite; no signs of concurrent infection; carers not planning to move in next 4 months Exclusion criteria: failure to obtain informed consent from carer; no fixed address; tuberculosis or any congenital/acquired disorder affecting growth; on exclusion diet for treatment of persistent diarrhoea; history of soy, peanut or milk protein allergy
Interventions	Arm 1: soy-based RUTF No other arm reported, but it is labelled a randomised clinical trial
Outcomes	Primary outcome: <ul style="list-style-type: none"> rate of weight gain (time frame: up to 3 years)
Starting date	July 2012
Contact information	Name: Iqbal Hossain, Bangladesh Email: ihossain@icddr.org
Notes	Location: Bangladesh Sponsor: not reported

NCT01705769

Trial name or title	From uncomplicated severe acute malnutrition (SAM) in India and to use the evidence to inform national policy
Methods	Randomised controlled trial, parallel group design
Participants	Inclusion criteria: aged 6-59 months; SAM defined as WHZ < -3 SD of WHO standard or oedema in both feet Exclusion criteria: complicated SAM requiring hospitalisation; known allergy to animal milk or peanuts; likely to leave study are in next 8 weeks
Interventions	Arm 1: RUTF commercially produced Arm 2: RUTF non-commercially produced (by the study team) Arm 3: high-energy and micronutrient rich foods
Outcomes	Primary outcome: <ul style="list-style-type: none"> recovery within 8 weeks defined as WHZ $\geq$ -2 SD and no oedema on feet Secondary outcomes: <ul style="list-style-type: none"> cost of interventions (time frame: enrolment until end of study) feedback from families and healthcare professionals about the interventions: perceptions and feasibility of use (time frame: enrolment until end of study)

NCT01705769 (Continued)

	<ul style="list-style-type: none"> • mortality (time frame: 4, 8 and 26 weeks after enrolment) • hospitalisation (time frame: 4, 8 and 26 weeks after enrolment) • proportion of children with diarrhoea (time frame: 4 weeks after enrolment) • proportion of children with WHZ ≥ -2 SD and no oedema on feet (time frame: 18 weeks after recovery) • rate of weight gain (g/kg/day) (time frame: 8 weeks or until recovery) • time to recovery (time frame: 8 weeks or until recovery)
Starting date	October 2012
Contact information	Name: Nita Bhandari, India
Notes	Location: India Sponsor: Action Research and Training for Health (ARTH), Udaipur; Christian Medical College, India; World Health Organization

NCT01785680

Trial name or title	Conducting research on moderate acute malnutrition in humanitarian emergencies: integrated management of MAM and SAM in Sierra Leone with ready to use therapeutic foods (RUTF)
Methods	Randomised clinical trial, parallel group design
Participants	Inclusion criteria: boys and girls with MAM or with non-complicated SAM; aged 6-59 months; acceptable appetite; only youngest child with malnutrition in each household will be enrolled - older MAM or SAM siblings will be treated operationally using the same protocol Exclusion criteria: children with obvious chronic debilitating illness (e.g. cerebral palsy or congenital abnormalities); children having received treatment for MAM or SAM in the previous 2 months
Interventions	Specific arms not reported, but RUTF is mentioned in the title
Outcomes	Primary outcome: <ul style="list-style-type: none"> • recovery (time frame: within 12 weeks) Secondary outcomes: <ul style="list-style-type: none"> • change in growth rates (time frame: 12 weeks, 6 months) • change in recovery status (time frame: 6 months) • cost estimate for participation (time frame: 12 weeks) • default reason (time frame: within 12 weeks) • duration of treatment (time frame: within 12 weeks)
Starting date	January 2013
Contact information	Name: Amanda Maust Email: amandamaust@gmail.com Name: Mark Manary, USA Email: manary@kids.wustl.edu

Notes	Location: Sierra Leone Sponsor: not reported
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kCal: kilocalories; MAM: moderate acute malnutrition; MUAC: mid-upper arm circumference; NCHS: National Center for Health Statistics; RUTF: ready-to-use therapeutic food; SAM: severe acute malnutrition; SD: standard deviation; WAZ: weight for age z score; WHO: World Health Organization; WHZ: weight for height z score.

DATA AND ANALYSES

Comparison 1. Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recovery	3	599	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.16, 1.50]
1.1 HIV-uninfected and untested children	2	534	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.10, 1.58]
1.2 HIV-infected children	1	65	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.97, 2.04]
2 Relapse	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 HIV-uninfected and untested children	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 HIV-infected children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality	3	599	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.46, 2.05]
3.1 HIV-uninfected and untested children	2	534	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.32, 1.88]
3.2 HIV-infected children	1	65	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.42, 6.85]
4 Weight gain (g/kg/day)	3	595	Mean Difference (IV, Random, 95% CI)	1.47 [0.49, 2.45]
4.1 HIV-uninfected and untested children	2	530	Mean Difference (IV, Random, 95% CI)	1.79 [0.65, 2.93]
4.2 HIV-infected children	1	65	Mean Difference (IV, Random, 95% CI)	0.80 [-0.64, 2.24]
5 Time to recovery for HIV-uninfected children (days)	1	136	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-15.89, 1.89]
6 Mid-upper arm circumference gain (mm/day)	3	570	Mean Difference (IV, Random, 95% CI)	0.13 [0.04, 0.21]
6.1 HIV-uninfected and untested children	2	505	Mean Difference (IV, Random, 95% CI)	0.15 [0.07, 0.24]
6.2 HIV-infected children	1	65	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.28, 0.20]
7 Weight for height z score at follow-up in HIV-uninfected children	1	99	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.22, 0.60]
8 Days of diarrhoea during the intervention period	1	352	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.30, 0.10]

Comparison 2. Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recovery	2	210	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.60, 0.84]
1.1 HIV-uninfected children	1	162	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.60, 0.87]
1.2 HIV-infected children	1	48	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.39, 0.99]
2 Relapse	2	210	Risk Ratio (M-H, Random, 95% CI)	8.95 [1.18, 67.77]
2.1 HIV-uninfected children	1	162	Risk Ratio (M-H, Random, 95% CI)	15.25 [0.91, 255.90]

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2.2 HIV-infected children	1	48	Risk Ratio (M-H, Random, 95% CI)	5.07 [0.28, 93.00]
3 Mortality	2	210	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.25, 2.18]
3.1 HIV-uninfected children	1	162	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.08, 2.81]
3.2 HIV-infected children	1	48	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.24, 3.80]
4 Weight gain (g/kg/day)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 HIV-uninfected children	1	158	Mean Difference (IV, Fixed, 95% CI)	-2.10 [-3.08, -1.12]
4.2 HIV-infected children	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.73, 1.53]
5 Time to recovery for HIV-uninfected children (days)	1	116	Mean Difference (IV, Fixed, 95% CI)	10.0 [0.87, 19.13]
6 Mid-upper arm circumference gain (mm/day)	2	173	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.22, 0.01]
6.1 HIV-uninfected children	1	125	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.27, -0.03]
6.2 HIV-infected children	1	48	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.20, 0.14]
7 Weight for height z score at follow-up for HIV-uninfected children	1	73	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.56, 0.36]

Comparison 3. Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recovery	1	1874	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.93, 1.01]
2 Relapse	1	1874	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.03, 1.72]
3 Mortality	1	1874	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.55, 1.45]
4 Weight gain (g/kg/day)	1	1874	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-0.75, -0.25]
5 Mid-upper arm circumference gain (mm/day)	1	1874	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.06, -0.02]
6 Weight for height z score	1	1874	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.10, 0.10]
7 Weight for age z score	1	1874	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.21, 0.01]
8 Height for age z score	1	1874	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.24, 0.04]

Analysis 1.1. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 1 Recovery.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 1 Recovery

Analysis 1.2. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 2 Relapse.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 2 Relapse

Analysis 1.3. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 3 Mortality.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 3 Mortality

Analysis 1.4. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 4 Weight gain (g/kg/day).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 4 Weight gain (g/kg/day)

Analysis 1.5. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 5 Time to recovery for HIV-uninfected children (days).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 5 Time to recovery for HIV-uninfected children (days)

Analysis 1.6. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 6 Mid-upper arm circumference gain (mm/day).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 6 Mid-upper arm circumference gain (mm/day)

Analysis 1.7. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 7 Weight for height z score at follow-up in HIV-uninfected children.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 7 Weight for height z score at follow-up in HIV-uninfected children

Analysis 1.8. Comparison 1 Ready-to-use therapeutic food (RUTF) versus standard diet, Outcome 8 Days of diarrhoea during the intervention period.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 1 Ready-to-use therapeutic food (RUTF) versus standard diet

Outcome: 8 Days of diarrhoea during the intervention period

Analysis 2.1. Comparison 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements), Outcome 1 Recovery.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome: 1 Recovery

Analysis 2.2. Comparison 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements), Outcome 2 Relapse.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome: 2 Relapse

Analysis 2.3. Comparison 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements), Outcome 3 Mortality.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome: 3 Mortality

Analysis 2.4. Comparison 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements), Outcome 4 Weight gain (g/kg/day).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome: 4 Weight gain (g/kg/day)

Analysis 2.5. Comparison 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements), Outcome 5 Time to recovery for HIV-uninfected children (days).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome: 5 Time to recovery for HIV-uninfected children (days)

Analysis 2.6. Comparison 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements), Outcome 6 Mid-upper arm circumference gain (mm/day).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome: 6 Mid-upper arm circumference gain (mm/day)

Analysis 2.7. Comparison 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements), Outcome 7 Weight for height z score at follow-up for HIV-uninfected children.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 2 Ready-to-use therapeutic food (RUTF) supplement versus RUTF (total daily requirements)

Outcome: 7 Weight for height z score at follow-up for HIV-uninfected children

Analysis 3.1. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 1 Recovery.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 1 Recovery

Analysis 3.2. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 2 Relapse.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 2 Relapse

Analysis 3.3. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 3 Mortality.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 3 Mortality

Analysis 3.4. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 4 Weight gain (g/kg/day).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 4 Weight gain (g/kg/day)

Analysis 3.5. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 5 Mid-upper arm circumference gain (mm/day).

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 5 Mid-upper arm circumference gain (mm/day)

Analysis 3.6. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 6 Weight for height z score.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 6 Weight for height z score

Analysis 3.7. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 7 Weight for age z score.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 7 Weight for age z score

Analysis 3.8. Comparison 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content, Outcome 8 Height for age z score.

Review: Ready-to-use therapeutic food for home-based treatment of severe acute malnutrition in children from six months to five years of age

Comparison: 3 Ready-to-use therapeutic food (RUTF) with reduced milk powder content versus RUTF with recommended milk powder content

Outcome: 8 Height for age z score

ADDITIONAL TABLES

Table 1. Classification of severe acute malnutrition in children under 60 months old (Collins 2006)

Severe acute malnutrition with complications	Severe acute malnutrition without complications
Bilateral pitting oedema grade 3*** (severe oedema) OR	MUAC < 110 [†] mm OR
MUAC < 110 [†] mm and bilateral pitting oedema grades 1* or 2** (marasmic kwashiorkor) OR	Bilateral pitting oedema grades 1* or 2** with MUAC ≥ 110 [†] mm AND <ul style="list-style-type: none"> • Appetite • Clinically well • Alert
MUAC < 110 [†] mm or bilateral pitting oedema grades 1* or 2** AND 1 of the following: <ul style="list-style-type: none"> • Anorexia • Lower-respiratory tract infection[□] • Severe palmar pallor • High fever • Severe dehydration • Not alert 	-

Table 1. Classification of severe acute malnutrition in children under 60 months old (Collins 2006) (Continued)

Inpatient care IMCI/WHO protocol	Outpatient therapeutic care protocols

IMCI: Integrated Management of Childhood Illness; MUAC: mid-upper arm circumference; UNICEF: United Nations Children's Fund; WHO: World Health Organization.

*Grade 1 = mild oedema on both feet or both ankles.

**Grade 2 = moderate oedema on both feet, and on lower legs, hands or lower arms.

***Grade 3 = severe generalised oedema affecting feet, legs, hands, arms and face.

†The WHO and UNICEF now recommend that the cut-off value for the MUAC for severe acute malnutrition should be increased to 115 mm (WHO and UNICEF 2009). The adoption of this higher cut-off value will sharply increase the caseloads, which may influence the cost of nutrition programmes greatly (WHO and UNICEF 2009). However, detecting more children earlier as severely malnourished will lead to a shorter period needed to treat them, which may bring down the cost per child (WHO and UNICEF 2009).

‡IMCI criteria: 60 respirations/min children age < 2 months; 50 respirations/min for age 2-12 months; 40 respirations/min for age 1-5 years; 30 respirations/min for age > 5 years.

Table 2. Nutritional composition of ready-to-use therapeutic food, as recommended by the World Health Organization (WHO 2007)

Moisture content	2.5% maximum
Energy	520-550 kCal/100 g
Protein	101-2% total energy
Lipids	45-60% total energy
Sodium	290 mg/100 g maximum
Potassium	1110-1400 mg/100 g
Calcium	300-600 mg/100 g
Phosphorus (excluding phytate)	300-600 mg/100 g
Magnesium	80-140 mg/100 g
Iron	10-14 mg/100 g
Zinc	11-14 mg/100 g
Copper	1.4-1.8 mg/100 g
Selenium	20-40 µg
Iodine	70-140 µg/100 g

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Table 2. Nutritional composition of ready-to-use therapeutic food, as recommended by the World Health Organization (WHO 2007) (Continued)

Vitamin A	0.8-1.1 mg/100 g
Vitamin D	15-20 µg/100 g
Vitamin E	20 mg/100 g minimum
Vitamin K	15 to 30 µg/100 g
Vitamin B1	0.5 mg/100 g minimum
Vitamin B2	1.6 mg/100 g minimum
Vitamin C	50 mg/100 g minimum
Vitamin B6	0.6 mg/100 g minimum
Vitamin B12	1.6 µg/100 g minimum
Folic acid	200 µg/100 g minimum
Niacin	5 mg/100 g minimum
Pantothenic acid	3 mg/100 g minimum
Biotin	60 µg/100 g minimum
n-6 fatty acids	3-10% of total energy
n-3 fatty acids	0.3-2.5% of total energy

Table 3. A typical recipe for ready-to-use therapeutic food (Manary 2006)

Ingredient	% weight
Full-fat milk	30
Sugar	28
Vegetable oil	15
Peanut butter*	25
Mineral-vitamin mix	1.6

*Strict quality control is essential.

Table 4. Recipe of RUTF-1: rice-sesame (Collins 2004)

Ingredient	Quantities (%)
Roasted rice flour	20
Soyamin 90	29
Roasted sesame seed paste	8
Sunflower oil	19.4
Icing sugar	22
Vitamin and mineral premix (CMV therapeutique, Nutriset)	1.6

RUTF: ready-to-use therapeutic food.

Table 5. Recipe of RUTF-2: barley-sesame (Collins 2004)

Ingredient	Quantities (%)
Roasted pearl barley flour	15
Soyamin 90	9
Roasted sesame seed paste	27
Sunflower oil	24
Icing sugar	23.4
Vitamin and mineral premix (CMV therapeutique, Nutriset)	1.6

RUTF: ready-to-use therapeutic food.

Table 6. Recipe of RUTF-3: maize-sesame (Collins 2004)

Ingredient	Quantities (%)
Roasted maize flour	33.4
Roasted sesame seed paste	27
Roasted chick pea flour	25

Table 6. Recipe of RUTF-3: maize-sesame (Collins 2004) *(Continued)*

Sunflower oil	12
Icing sugar	15
Vitamin and mineral premix (CMV therapeutique, Nutriset)	1.6

RUTF: ready-to-use therapeutic food.

Table 7. Nutritional information of various ready-to-use therapeutic food (RUTF) recipes (Collins 2004)

Nutrient	Unit	RUTF-1 (100 g)	Energy (%)	RUTF-2 (100 g)	Energy (%)	RUTF-3 (100 g)	Energy (%)	Plumpy'nut® (100 g)	Energy (%)
Energy**	kCal	551	-	567	-	512	-	530	-
Energy	kJ	2307	-	2373	-	2142	-	2218	-
Protein	g	13.8	10	14.1	10	13.4	11	14.5	11
Carbohydrate***	g	43	31	39.9	28	50.2	39	43	32
Fat	g	36	59	39	62	28.6	50	33.5	57
Ash	g	43	-	3.9	-	4.9	-	4	-
Moisture	g	2.9	-	3.1	-	2.9	-	< 5	-

*Protein and fat are reported to contribute 11% and 57% in energy input, respectively. Total energy is reported to be 530 kcal/100 g and moisture < 5%.

**The energy has been calculated using Atwater factors.

***Carbohydrate is by difference assuming protein to be nitrogen multiplied by 6.25.

Table 8. Mineral content of various ready-to-use therapeutic food (RUTF) recipes (Collins 2004)

Mineral	RUTF-1 (mg/kg)	RUTF-2 (mg/kg)	RUTF-3 (mg/kg)	Plumpy'nut®(mg/kg)
Cu	2.1	2.1	1.8	1.7
Zn	10.9	10.9	10.2	13
Ca	338.1	338.1	209.8	310

Table 8. Mineral content of various ready-to-use therapeutic food (RUTF) recipes (Collins 2004) (Continued)

Na	256.5	256.5	189.9	< 290
Mg	118.4	118.4	119.1	86
Fe	5.6	5.6	4.4	12.45

Table 9. Water activity in various ready-to-use therapeutic food (RUTF) recipes (Collins 2004)

RUTF recipe	Water activity
RUTF-1	0.290
RUTF-2	0.279
RUTF-3	0.260
Plumpy'nut®	0.241

Table 10. Severe acute malnutrition management as recommended by the WHO and UNICEF (WHO and UNICEF 2009)

Independent additional criteria	<ul style="list-style-type: none"> • No appetite • Medical complications 	<ul style="list-style-type: none"> • Appetite • No medical complications
Type of therapeutic feeding	Facility-based	Community-based
Intervention	<ul style="list-style-type: none"> • F75 (Phase 1) • F100/RUTF (Phase 2) • And 24-hour medical care 	<ul style="list-style-type: none"> • RUTF • And basic medical care
Discharge criteria (transition criteria from facility to community-based care)	<ul style="list-style-type: none"> • Reduced oedema • Good appetite (with acceptable* intake of RUTF) 	<ul style="list-style-type: none"> • 15-20% weight gain

RUTF: ready-to-use therapeutic food; UNICEF: United Nations Children's Fund; WHO: World Health Organization.

*Children who eat at least 75% of their calculated RUTF ration for the day.

Table 11. Classification of attrition from included studies

Study ID	Participants recruited (n)	Pre-randomisation attrition (n)	Immediately post-randomisation attrition (n)	Drop-outs during the intervention period (n)
Ciliberto 2005	1178 (includes moderate and severe malnourished children)	0	41 (reasons not reported)	72 (reasons not reported)
Manary 2004	452	77 refused 93 HIV positive	0	47 were “dropouts” (no reasons reported) and 37 died (no reasons reported)
Ndekha 2005	93	0	0	11 died (no reasons reported) and 17 drop-outs (no reasons reported)
Oakley 2010	1961	87 (reasons not reported)	0	51 were lost to follow-up (no reasons reported other than “those lost were more likely to be younger and marasmic”)

Table 12. Additional assessment of risk of bias in the included cluster-randomised trials

Study ID	Recruitment bias	Baseline imbalance	Loss of clusters
Ciliberto 2005	Inadequate Being a stepped wedge design, recruitment occurred after sites were assigned a specific treatment. All children eventually ended up with RUTF, although the time point at which conversion from standard care to RUTF took place was unknown The study authors recognised that recruitment bias was possible: “a source of bias might have been that a mother of a moderately malnourished child might have visited the NRU for screening when she heard that home-based therapy was being offered”	Unclear Baseline characteristics per intervention arm were reported (significant difference in terms of WHZ), but similarities and differences between clusters were not mentioned	Adequate All randomised children were included in the analyses
Manary 2004	Adequate Children were recruited after discharge days were allocated to a specific treatment. However, an independent doctor discharged the children unknowingly which dis-	Unclear Baseline characteristics per intervention arm were reported, but similarities and differences between children discharged on different days were not mentioned	Adequate All randomised children were included in the analyses

Table 12. Additional assessment of risk of bias in the included cluster-randomised trials (Continued)

	charge days matched which treatment. Therefore, the risk of recruitment bias was minimised		
Ndekha 2005	Adequate Children were recruited after the weeks of discharge were allocated to a specific treatment. However, an independent doctor discharged the children unknowingly which discharge weeks matched which treatment. Therefore, the risk of recruitment bias was minimised	Unclear Baseline characteristics per intervention arm were reported, but similarities and differences between children discharged during different weeks were not mentioned	Adequate All randomised children were included in the analyses

NRU: nutrition rehabilitation unit; RUTF: ready-to-use therapeutic food; WHZ: weight for height z score.

Table 13. Evaluating the methodological quality of systematic reviews with the AMSTAR tool (Shea 2007)

	Yes/No/Can't answer/Not applicable	
Criteria	Gera 2010	Our RUTF review
1. Was an 'a priori' design provided? - The research question and inclusion criteria should be established before the conduct of the review	Yes	Yes
2. Was there duplicate study selection and data extraction? - There should be at least 2 independent data extractors and a consensus procedure for disagreements should be in place	No	Yes
3. Was a comprehensive literature search performed? - At least 2 electronic sources should be searched. The report must include years and databases used (e.g. CENTRAL, EMBASE and MEDLINE). Key words or MESH terms, or both must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialised registers or experts in the particular field of study, and by reviewing	Incomplete - CENTRAL and MEDLINE were searched with 4 different search terms (no search strings) on 20 April 2010. This electronic database search was not supplemented by screening reference lists and contacting researchers/clinicians in the field	Yes

Table 13. Evaluating the methodological quality of systematic reviews with the AMSTAR tool (Shea 2007) (Continued)

the references in the studies found		
<p>4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?</p> <p>- The authors should state that they searched for reports regardless of their publication type.</p> <p>The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language, etc</p>	<p>Can't answer, nothing about publication and language was reported</p>	No
<p>5. Was a list of studies (included and excluded) provided?</p> <p>- A list of included and excluded studies should be provided</p>	<p>No</p> <p>- A list of excluded studies was not reported</p>	Yes
<p>6. Were the characteristics of the included studies provided?</p> <p>- In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes.</p> <p>The ranges of characteristics in all the studies analysed (e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity or other diseases) should be reported</p>	<p>No</p> <p>- A list of included studies was provided but it did not contain all relevant information (e.g. characteristics of participants, interventions, control)</p>	Yes
<p>7. Was the scientific quality of the included studies assessed and documented?</p> <p>- A priori methods of assessment should be provided (e.g. for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant</p>	No	Yes
<p>8. Was the scientific quality of the included studies used appropriately in formulating conclusion?</p> <p>- The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations</p>	No	Yes

Table 13. Evaluating the methodological quality of systematic reviews with the AMSTAR tool (Shea 2007) (Continued)

9. Were the methods used to combine the findings of studies appropriate? - For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi ² test for homogeneity, I ² statistic). If heterogeneity exists a random effects model should be used or the clinical appropriateness of combining should be taken into consideration, or both (i.e. is it sensible to combine?)	No - 2 meta-analyses were performed, 1 that was accompanied by a I ² value of 89.8% and 1 did not report an I ² value. The term 'heterogeneity' did not appear in the article. In addition, the software used to conduct the meta-analyses was not reported and nothing mentioned about the effects model (i.e. fixed or random) used	Yes
10. Was the likelihood of publication bias assessed? - An assessment of publication bias should include a combination of graphical aids (e.g. funnel plot, other available tests) or statistical tests (e.g. Egger regression test), or both	No - Publication bias was not mentioned in the article	Not applicable - We set out in our protocol to assess the likelihood of publication bias, but since we had too few studies per comparison we could not draw a funnel plot
11. Was the conflict of interest stated? - Potential sources of support should be clearly acknowledged in both the systematic review and the included studies	Yes - The author declared that she had no competing interests and she stated that there was no funding	Yes

APPENDICES

Appendix I. Search strategies

CENTRAL Searched 30 November 2010, 26 April 2012 and 4 April 2013

- #1 MeSH descriptor Nutrition Disorders, this term only
- #2 MeSH descriptor Child Nutrition Disorders, this term only
- #3 MeSH descriptor Infant Nutrition Disorders, this term only
- #4 MeSH descriptor Protein-Energy Malnutrition, this term only
- #5 MeSH descriptor Wasting Syndrome, this term only
- #6 MeSH descriptor Emaciation, this term only
- #7 undernutrition or under-nutrition
- #8 undernourish* or under-nourish*
- #9 malnutrition or mal-nutrition
- #10 malnourish* or mal-nourish*
- #11 nutrition* NEXT defic*
- #12 marasmus
- #13 kwashiorkor
- #14 emaciat*
- #15 wasted or wasting

#16 stunted or stunting
 #17 MeSH descriptor Malnutrition, this term only
 #18 MeSH descriptor Deficiency Diseases, this term only
 #19 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)
 #20 MeSH descriptor Food, Formulated, this term only
 #21 MeSH descriptor Dietary Supplements explode all trees
 #22 therapeutic Near/3 (food* or diet*)
 #23 enrich* Near/3 (food* or diet*)
 #24 fortifi* Near/3 (food* or diet*)
 #25 supplement* Near/3 (food* or diet*)
 #26 ready Near/3 food*
 #27 RUTF
 #28 RTUF
 #29 ready-to-use food
 #30 MeSH descriptor Food, Fortified, this term only
 #31 (#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #29 OR #30)
 #32 baby or babies or infant* or child* or boy* or girl* or toddler* or preschool* or pre-school* or kindergarten*
 #33 (#19 AND #31 AND #32)

Ovid MEDLINE(R) 1946 to April week 4 2013 Searched 30 November 2010, 26 April 2012 and 4 April 2013

1 nutrition disorders/
 2 malnutrition/
 3 exp protein-energy malnutrition/
 4 wasting syndrome/
 5 Emaciation/
 6 infant nutrition disorders/
 7 child nutrition disorders/
 8 deficiency diseases/
 9 (undernutrition or under-nutrition).tw.
 10 (undernourish\$ or under-nourish\$).tw.
 11 (malnutrition or mal-nutrition).tw.
 12 (malnourish\$ or mal-nourish\$).tw.
 13 (nutrition\$ adj defic\$).tw.
 14 marasmus\$.tw.
 15 kwashiorkor.tw.
 16 emaciat\$.tw.
 17 (wasted or wasting).tw.
 18 (stunted or stunting).tw.
 19 or/1-18
 20 Food, Fortified/
 21 Food, Formulated/
 22 exp Dietary Supplements/
 23 (therapeutic adj3 (food\$ or diet\$)).tw.
 24 (enrich\$ adj3 (food\$ or diet\$)).tw.
 25 (fortifi\$ adj3 (food\$ or diet\$)).tw.
 26 (supplement\$ adj3 (food\$ or diet\$)).tw.
 27 (ready adj3 food\$).tw.
 28 (RUTF or RTUF).tw.
 29 or/20-28
 30 19 and 29
 31 Infant/
 32 exp Child/

33 (baby or babies or infant\$ or child\$ or boy\$ or girl\$ or toddler\$ or preschool\$ or pre-school\$ or kindergarten\$).tw.
 34 31 or 32 or 33
 35 30 and 34
 36 randomized controlled trial.pt.
 37 controlled clinical trial.pt.
 38 randomi#ed.ab.
 39 placebo\$.ab.
 40 drug therapy.fs.
 41 randomly.ab.
 42 trial.ab.
 43 groups.ab.
 44 or/36-43
 45 exp animals/ not humans.sh.
 46 44 not 45
 47 35 and 46

EMBASE (Ovid) 1980 to 2013 week 13 Searched 30 November 2010, 24 April 2012 and 4 April 2013

1 nutritional deficiency/
 2 nutritional disorder/
 3 protein calorie malnutrition/
 4 malnutrition/
 5 wasting syndrome/
 6 weight reduction/
 7 (undernutrition or under-nutrition).tw.
 8 (undernourish\$ or under-nourish\$).tw.
 9 (malnutrition or mal-nutrition).tw.
 10 (malnourish\$ or mal-nourish\$).tw.
 11 (nutrition\$ adj defic\$).tw.
 12 emaciat\$.tw.
 13 (wasted or wasting).tw.
 14 (stunted or stunting).tw.
 15 kwashiorkor/
 16 kwas?io?kor.tw.
 17 marasmus/
 18 marasmus\$.tw.
 19 or/1-18
 20 diet supplementation/
 21 "ready to use therapeutic food"/
 22 (therapeutic adj3 (food\$ or diet\$)).tw.
 23 (fortifi\$ adj3 (food\$ or diet\$)).tw.
 24 (enrich\$ adj3 (food\$ or diet\$)).tw.
 25 (supplement\$ adj3 (food\$ or diet\$)).tw.
 26 (ready adj3 food\$).tw.
 27 (RUTF or RTUF).tw.
 28 or/20-27
 29 infant/
 30 exp child/
 31 (baby or babies or infant\$ or child\$ or boy\$ or girl\$ or toddler\$ or preschool\$ or pre-school\$ or kindergarten\$).tw.
 32 29 or 30 or 31
 33 Clinical trial/
 34 Randomized controlled trial/
 35 Randomization/
 36 Single blind procedure/

37 Double blind procedure/
 38 Crossover procedure/
 39 Placebo/
 40 Randomi#ed.tw.
 41 RCT.tw.
 42 (random\$ adj3 (allocat\$ or assign\$)).tw.
 43 randomly.ab.
 44 groups.ab.
 45 trial.ab.
 46 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
 47 Placebo\$.tw.
 48 Prospective study/
 49 (crossover or cross-over).tw.
 50 prospective.tw.
 51 or/33-50
 52 19 and 28 and 32 and 51

Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations Searched 24 April 2012 and 4 April 2013

1 (undernutrition or under-nutrition).tw.
 2 (undernourish\$ or under-nourish\$).tw.
 3 (malnutrition or mal-nutrition).tw.
 4 (malnourish\$ or mal-nourish\$).tw.
 5 (nutrition\$ adj defic\$).tw.
 6 marasmus\$.tw.
 7 kwashiorkor.tw.
 8 emaciat\$.tw.
 9 (wasted or wasting).tw.
 10 (stunted or stunting).tw.
 11 or/1-10
 12 (therapeutic adj3 (food\$ or diet\$)).tw.
 13 (enrich\$ adj3 (food\$ or diet\$)).tw.
 14 (fortifi\$ adj3 (food\$ or diet\$)).tw.
 15 (supplement\$ adj3 (food\$ or diet\$)).tw.
 16 (ready adj3 food\$).tw.
 17 (RUTF or RTUF).tw.
 18 or/12-17
 19 (baby or babies or infant\$ or child\$ or boy\$ or girl\$ or toddler\$ or preschool\$ or pre-school\$ or kindergarten\$).tw.
 20 11 and 18 and 19

CINAHL (EBSCOhost) 1937 to current Searched 1 December 2010, 26 April 2012 and 8 April 2013

S33 S18 and S27 and S32
 S32 S28 or S29 or S30 or S31
 S31 TI(baby or babies or infant* or child* or boy* or girl* or toddler* or preschool* or pre-school* or kindergarten*)
 S30 AB(baby or babies or infant* or child* or boy* or girl* or toddler* or preschool* or pre-school* or kindergarten*)
 S29 AG Infant: 1-23 months
 S28 AG child,preschool
 S27 (S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26)
 S26 RUTF or RTUF
 S25 ready N3 food*
 S24 (supplement* N3 food*) or (supplement* N3 diet*)
 S23 (fortifi* N3 food*) or (fortifi* N3 diet*)
 S22 (therapeutic N3 food*) or (therapeutic N3 diet*)
 S21 (enrich N3 food*) or (enrich N3 diet*)

S20 (MH "Dietary Supplements")
 S19 (MH "Food, Fortified")
 S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
 S17 (stunted or stunting)
 S16 (wasted or wasting)
 S15 emaciat*
 S14 kwashiorkor*
 S13 marasmus*
 S12 (malnourish* or mal-nourish*)
 S11 (nutrition defic*)
 S10 (malnutrition or mal-nutrition)
 S9 (undernourish* or under-nourish*)
 S8 (undernutrition or under-nutrition)
 S7 (MH "Kwashiorkor")
 S6 (MH "Deficiency Diseases")
 S5 (MH "Protein-Energy Malnutrition")
 S4 (MH "Protein Deficiency")
 S3 (MH "Infant Nutrition Disorders")
 S2 (MH "Child Nutrition Disorders")
 S1 (MH "Nutrition Disorders")

African Index Medicus Searched 26 April 2012 and 8 April 2013

Search on : "INFANT NUTRITION DISORDERS" or "CHILD NUTRITION DISORDERS" or "MALNUTRITION" or "EMACIATION" or "KWASHIORKOR" or "MARASMUS" or wasting or wasted or stunting or stunted or emaciat\$ [Key Word] and "CHILD" or "infant" or baby or babies or bebe\$ or enfant\$ or preschool\$ [Key Word]

LILACS Searched 26 April 2012 and 8 April 2013

(Mh "malnutrition" or Mh "wasting syndrome" or Mh "protein-energy malnutrition" or Mh "Emaciation" or Mh "infant nutrition disorders" or Mh "child nutrition disorders" or Mh "deficiency diseases" or Tw kwashiorkor or Tw marasmus or Tw emaciat\$ or Tw wasting or Tw wasted or Tw stunting or Tw stunted) [Words] and (Tw child\$ or Tw baby or Tw babies or Tw infan\$ or Tw enfant\$ or Tw bebe\$ or Mh "child, PRESCHOOL" or Mh "INFANT") [Words] and ((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) OR (Pt clinical trial OR Ex E05.318.760.535\$ OR (Tw clin\$ AND (Tw trial\$ OR Tw ensa\$ OR Tw estud\$ OR Tw experim\$ OR Tw investiga\$)) OR ((Tw singl\$ OR Tw simple\$ OR Tw doubl\$ OR Tw doble\$ OR Tw duplo\$ OR Tw trebl\$ OR Tw trip\$) AND (Tw blind\$ OR Tw cego\$ OR Tw ciego\$ OR Tw mask\$ OR Tw mascar\$)) OR Mh placebos OR Tw placebo\$ OR (Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337\$ OR Mh follow-up studies OR Mh prospective studies OR Tw control\$ OR Tw prospectiv\$ OR Tw volunt\$ OR Tw volunteer\$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) [Words]

ZETOC Searched 26 April 2012 and 8 April 2013

Limited to Conference search using:

RUTF

RTUF

"therapeutic food"

"ready to use food"

WHO ICTRP Searched 12 May 2010, 26 April 2012 and 8 April 2013

RUTF OR RTUF OR therapeutic food OR ready to use food

metaRegister Searched 5 December 2010, 26 April 2012 and 8 April 2013
RUTF or RTUF or “therapeutic food” or “ready to use food”

Clinicaltrials.gov Searched 5 December 2010, 26 April 2012 and 8 April 2013
RUTF OR therapeutic food OR ready to use food

Appendix 2. Assessment of risk of bias in included RCTs

Domain 1: sequence generation (Higgins 2008)

Adequate: investigators described a random component in the sequence generation process such as the use of:

- a random number table;
- coin tossing;
- throwing dice;
- shuffling cards or envelopes.

Inadequate: investigators described a non-random component in the sequence generation process such as the use of:

- odd or even date of birth;
- the day or date of admission;
- the hospital or clinic record number;
- preference of the participant;
- the results of a laboratory test or series of tests.

Unclear: there is insufficient information to permit judgement of the way in which sequence generation was performed.

Domain 2: allocation concealment (Higgins 2008)

Adequate: neither participants nor investigators enrolling participants could foresee assignment due to:

- central allocation (e.g. via the telephone or pharmacy-controlled);
- sequentially numbered drug containers of a matching appearance;
- sequentially numbered, opaque and sealed envelopes.

Inadequate: both participants and investigators enrolling participants could foresee upcoming assignment based on, for example:

- using an open random allocation schedule;
- assigned envelopes were unsealed, non-opaque or not numbered appropriately;
- date of birth;
- case record number.

Unclear: there is insufficient information to permit judgement to the sequence generation process.

Domain 3: blinding (Higgins 2008)

Adequate: when any one of the following are applicable:

- no blinding, but the review authors judge that the outcome would not be influenced by a lack of blinding;
- blinding of both the key study personnel and participants are ensured, and it is unlikely that blinding could have been broken;
- either participants or some key study personnel were not blinded, but the outcome measurement was blinded and the non-blinding of others are not likely to introduce bias.

Inadequate: when any one of the following is applicable:

- no blinding or incomplete blinding;
- blinding of key study personnel and participants were attempted, but it is likely that the blinding could have been broken;
- either key study personnel or participants were not blinded, which is likely to introduce bias.

Unclear: there is insufficient information to permit judgement, or the study did not address this outcome at all.

Domain 4: incomplete outcome data (Higgins 2008)

Adequate: when any one of the following is applicable:

- no missing outcome data;
- the reasons for missing outcome data are unlikely to be related to the true outcome;
- missing outcome data are balanced in numbers across intervention groups;
- missing data have been imputed using appropriate methods;

- for dichotomous data, the proportion of missing outcomes compared with the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate;
- for continuous data, the plausible effect size among missing outcomes is not enough to have a clinically relevant impact on the observed effect size.

Inadequate: when any one of the following is applicable:

- the reasons for missing outcome data are likely to be related to true outcome;
- the application of simple imputation is potentially inappropriate;
- 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
- for dichotomous data, the proportion of missing outcomes compared with the observed event risk is enough to introduce clinically relevant bias in the intervention effect estimate;
- for dichotomous outcome data, the plausible effect size among missing outcomes is enough to induce clinically relevant bias in the observed effect size.

Unclear: there is insufficient reporting of exclusions to permit judgement, or the study did not address this outcome at all.

Domain 5: selective outcome reporting (Higgins 2008)

Adequate: when any one of the following is applicable:

- the study protocol is available and all of the prespecified outcomes are addressed in the review in the prespecified way;
- the study protocol is not available, but it is clear that the published reports include all the prespecified and expected outcomes.

Inadequate: when any one of the following is applicable:

- not all of the prespecified primary outcomes have been reported;
- one or more of the primary outcomes is reported using measurements of analysis methods that were not prespecified;
- one or more reported primary outcomes were not prespecified;
- one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear: there is insufficient information to permit judgement of compliance.

Domain 6: other potential threats to validity (Higgins 2008)

Adequate: when the study seems to be free of other sources of bias.

Inadequate: when there is the possibility of at least one important risk of bias such as:

- the quality of the specific study design is in question;
- the study is stopped early due to some data-dependent process;
- the study has been claimed to have been fraudulent.

Unclear: when there may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists;
- insufficient rationale or evidence that an identified problem will introduce bias.

Appendix 3. Additional assessment of risk of bias in included cluster-randomised trials

Domain 1: recruitment bias

Recruitment bias can occur when individuals are recruited to the trial after the clusters have been randomised (Higgins 2008). The types of participants recruited can be influenced by the knowledge of whether the specific cluster is an intervention or a control cluster.

- Adequate: when no recruiting was done after randomisation.
- Inadequate: when additional recruiting was done after randomisation.
- Unclear: when no reporting was done regarding the timing of recruiting all participants.

Domain 2: baseline imbalance

Cluster-randomised trials often randomise all clusters at once, therefore, a lack of allocation concealment should not usually be a problem (Higgins 2008). However, when there is only a small number of clusters, there is a possibility of chance baseline imbalances between the randomised groups. This may affect either the clusters or the individuals.

- Adequate: when the baseline comparability of clusters is sufficient, or when statistical adjustment for baseline characteristics occurred (Higgins 2008).
- Inadequate: when there are significant differences between clusters and no statistical adjustments for baseline characteristics were made accordingly.

- Unclear: when no reporting was done regarding baseline characteristics, or when it is not clear whether the differences between the clusters were significant.

Domain 3: loss of clusters

It is possible that complete clusters may be lost from a trial, and have to be omitted from the analysis (Higgins 2008). In the same way as for missing outcome data in individually randomised trials, this may lead to bias in cluster-randomised trials. In addition, missing outcomes for individuals within clusters may also lead to a risk of bias in cluster-randomised trials.

- Adequate: there were no missing data, or the missing data were addressed in the correct manner.
- Inadequate: there were missing data and it was dealt with in a way that could have introduced bias.
- Unclear: when no reporting was done regarding missing data (either complete clusters or individuals within clusters), or when it is unclear whether the authors of the primary study have dealt with the missing data adequately (e.g. acceptable statistical adjustments).

FEEDBACK

Controversial sentence in Conclusion section, 3 March 2017

Summary

On 3 March 2017, Professor Paul Garner (UK) submitted the following criticism to Cochrane publishers Wiley-Blackwell:

"In the abstract, the authors state: Given the limited evidence base currently available, it is not possible to reach definitive conclusions regarding differences in clinical outcomes in children with severe acute malnutrition who were given home-based ready-to-use therapeutic food (RUTF) compared to the standard diet, or who were treated with RUTF in different daily amounts or formulations. They then conclude: For this reason, either RUTF or flour porridge can be used to treat children at home depending on availability, affordability and practicality. However, it is not possible to reach this conclusion BASED ON THE EVIDENCE. So the evidence does not say this. The evidence says, we don't know which is best."

Do you have any affiliation with or involvement in any organisation with a financial interest in the subject matter of your comment?

"I run the RPC that helped fund this review."

Reply

On 28 March 2017, the review author team responded as follows:

"Thanks for the comment. We meant that, in light of the poor quality of evidence for the effectiveness of RUTF, the decision about what home-based intervention to use could be based on factors such as what is available, affordable and practical in specific settings and contexts. We accept that the sentence could be incorrectly interpreted to mean that there is no difference between RUTF and flour porridge and have therefore deleted the sentence from the abstract, the plain language summary and from the conclusion. We have also begun the process of updating this review to incorporate new evidence."

Contributors

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(on behalf of the author team: Anel Schoonees, Martani Lombard, Alfred Musekiwa, Etienne Nel and Jimmy Volmink)

WHAT'S NEW

Last assessed as up-to-date: 30 May 2013.

Date	Event	Description
28 March 2017	Amended	A sentence that may have led to controversy has been removed from the concluding parts of the abstract, plain language summary and implications for practice sections

CONTRIBUTIONS OF AUTHORS

AS initiated and developed the idea. AS and JV wrote the protocol while ML and EN provided input. AS and ML screened the search outputs for eligibility and gave reasons for exclusion. AS, ML and AM extracted data and assessed risk of bias for each included study. AS and ML conducted the analyses and wrote the Results section with input from AM. AS and ML wrote the Discussion and Conclusion sections. All authors provided input in the final draft of this systematic review.

DECLARATIONS OF INTEREST

- Anel Schoonees - none known.
- Martani Lombard - none known.
- Alfred Musekiwa - none known.
- Etienne Nel - none known.
- Jimmy Volmink - none known.

SOURCES OF SUPPORT

Internal sources

- Food Security Initiative within the HOPE project, Stellenbosch University, South Africa.
- Effective Health Care Research Consortium, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol of this review was published in the February 2011 issue of *The Cochrane Library* with the title “Ready-to-use therapeutic food for treating undernutrition in children from 6 months to 5 years of age”. The objectives were “to assess the effects of RUTF on health outcomes such as recovery rate, relapse during the intervention period, anthropometrical status, weight gain and mortality in children with moderate or severe undernutrition.” Therefore, we originally planned to include both MAM and SAM children and include RUTF treatment in facilities and at home. In June 2012 the first review author (AS) presented the draft findings of this review at the South African Cochrane Centre’s monthly Cochrane Busting Session, which was attended by national and international researchers doing work, including Cochrane reviews, on priority topics in low- and middle-income countries. Questions about the scope of our RUTF review were raised. RUTF was originally developed as a home-based alternative to the more expensive facility-based treatment of children with SAM. In rural areas where people reside far from healthcare facilities, home-based treatment is more practical. In addition, from a health system’s perspective, it is important to know whether the cheaper RUTF regimen (RUTF as a supplement rather than RUTF meeting daily nutritional requirements) and formulation (reduced milk powder content) can achieve similar or better health outcomes. From a nutritional perspective, it is important that the children’s carers sustain and improve culture-specific dietary habits instead of relying solely on provided medical nutritional therapy. Therefore, after a few weeks of discussion with various stakeholders, we decided to change the scope of our RUTF review to include only *home-based* RUTF treatment, as well as only focus on *SAM* children. We assessed the treatment effects of home-based RUTF compared to standard diet in children with SAM, and also investigated whether a cheaper RUTF treatment (in smaller amounts or using a cheaper recipe) can achieve similar health outcomes than conventional RUTF. Our review will thus not overlap with the Cochrane review by Lazzerini et al, which is in progress, which is evaluating the “safety and effectiveness of different types of foods for children with moderate acute malnutrition (MAM) in low- and middle-income countries” (Lazzerini 2012).

Apart from the scope of the review, we also made the following small amendments. First, we changed the first primary outcome “recovery rate as defined by the study authors” to “recovery as defined by the study authors” as this is a more inclusive outcome. In none of the included studies’ recovery was reported as a rate. In future, if studies provided results for ‘recovery rate’ it will also be included in our review. We did not want to limit the outcome to studies that reported data for ‘recovery rate’. Second, in our protocol it was stated that we would report on the outcomes “deterioration or relapse during the intervention period as defined by study authors”. We felt that relapse at follow-up is also important because it is an indication whether the treatment versus control have a longer-term effect. We thus added the words “and beyond” to this outcome so that it now reads “deterioration or relapse during and beyond the intervention period as defined by the study authors”. Third, we added “time to recovery (duration of rehabilitation)” as a second secondary outcome as from an economical view point it is a useful outcome. From a clinical view point, it is also valuable because the sooner the malnourished child recovers, the sooner s/he can grow and develop optimally.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fast Foods; Acute Disease; Malawi; Malnutrition [*diet therapy; mortality]; Publication Bias; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Child, Preschool; Humans; Infant