Optimising the dosage of ready-to-use therapeutic food in children with uncomplicated severe acute malnutrition in the Democratic Republic of the Congo: a non-inferiority, randomised controlled trial

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Summary

Background Current standard management of severe acute malnutrition uses ready-to-use therapeutic food (RUTF) at a single weight-based calculation resulting in an increasing amount of RUTF provided to the family as the child's weight increases during recovery. Using RUTF at a gradually reduced dosage as the child recovers could reduce costs while achieving similar growth response.

Methods We conducted an open-label, non-inferiority, randomised controlled trial in the Democratic Republic of the Congo. Children aged 6–59 months with a mid-upper-arm circumference (MUAC) of less than 115 mm or a weight-for-height z-score (WHZ) of less than −3 or bipedal oedema and without medical complication were randomly assigned (1:1 ratio) using a specially developed software and random blocks (size was kept confidential), to either the current standard treatment (increasing the RUTF amount with increasing weight) or the OptiMA strategy (decreasing the RUTF dose with increasing weight and MUAC). The main endpoint was proportion of children who achieved recovery over the 6 months follow up period, as defined as meeting the following criteria for two consecutive weeks after a minimum of 4 weeks' treatment: axillary temperature less than 37.5 °C, no bipedal oedema, and anthropometric improvement (either MUAC 125 mm or greater or WHZ −1.5 or higher). We performed analyses on the intention-to-treat (ITT) (all children) and per-protocol populations (participants who had a minimum prescription of 4 weeks' RUTF, received at least 90% of the total amount of RUTF they were supposed to receive as per the protocol, and had a maximum interval of 6 weeks between any two visits in the 6-month follow-up). The non-inferiority margin was 10%. This trial is registered at ClinicalTrials.gov, and is now closed NCT03751475.

Findings Between July 22, 2019, and January 20, 2020, 491 children were randomly assigned, of whom 482 were analysed (240 in the standard group and 242 in the OptiMA group). In the ITT analysis, 234 (98%) children in the standard group and 231 (96%) children in OptiMA recovered (difference 2.0%, 95% CI −2.0% to 6.4%). In the PP analysis, 234 (98%) children in the standard group and 228 (97%) in OptiMA recovered (difference 1.3%, 95% CI −2.3% to 5.1%). Sensitivity analyses applying the same anthropometric recovery criteria to each group also showed non-inferiority of the OptiMA strategy in ITT and PP analysis.

Interpretation This non-inferiority trial treating uncomplicated children with MUAC of less than 115 mm or a WHZ of less than −3 or bipedal oedema with decreasing RUTF dose as MUAC and weight increase demonstrated non-inferiority compared to the standard protocol in a highly food-insecure context in the Democratic Republic of the Congo. These findings add evidence on the safety of RUTF dose reduction with significant RUTF cost savings.

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Translation For the French translation of the abstract see Supplementary Materials section.

Keywords: Severe acute malnutrition; Children; Ready-to-use therapeutic food; Africa; Randomized clinical trial

Research in context

Evidence before this study

We searched PubMed on May 9, 2021, for publications in English using the search terms "severe acute malnutrition" AND "randomised controlled trial". There were no date restrictions. Of the 176 study results, only one reported a trial comparing the standard ready-to-use therapeutic food (RUTF) dosage with a reduction in RUTF dosage in children with severe acute malnutrition.

Added value of this study

To our knowledge this is the first individual randomised controlled trial to compare a reduced RUTF dosage in children with severe acute malnutrition in the Democratic Republic of the Congo. We compared, over a 6 month period, the current national standard strategy (separate protocols and products for severe and moderate acute malnutrition using RUTF at an increasing amount as weight increases in children with severe acute malnutrition, and ready-to-use supplementary food at a fixed dose for children with moderate acute malnutrition) and the OptiMA strategy (a single protocol for severe and moderate acute malnutrition using only RUTF at a decreasing dose as weight and mid-upper-arm circumference (MUAC) improves) in children with uncomplicated severe acute malnutrition. We found that the proportion of children recovered over the 6-month follow-up in the trial was non-inferior in the OptiMA group (96%) compared to the standard group (98%). There was no significant difference between groups in terms of hospitalisations.

Implications of all the available evidence

These findings from an individual randomised controlled trial, together with those from one previous randomised controlled trial in Burkina-Faso show that a strategy of decreasing RUTF dose during treatment as a child's MUAC and weight increase is safe in children with uncomplicated severe acute malnutrition in a highly food-insecurity context.

Introduction

The World Health Organisation (WHO) defines severe acute malnutrition in children aged 6–59 months as either a mid-upper-arm circumference (MUAC) less than 115 mm, a weight-for-height z score (WHZ score) less than –3, or the presence of bilateral pitting oedema.[1] Globally, 13.6 million children aged under five are affected, with 3 million living in sub-Saharan Africa and 10.6 million in Asia.[2] In 2013, an estimated 7.4% of all deaths in children under five were attributable to severe acute malnutrition[3] Today, as few as 30% of eligible children receive treatment[4] partially due to chronically underfunded programmes.[5]

Children with severe acute malnutrition and no medical complications are treated with ready-to-use therapeutic food (RUTF), a highly fortified energy-dense paste that has been shown to be effective in the rehabilitation of children with severe wasting in outpatient care.[6] Current weight-based RUTF dosage (approximately 175 kcal/kg per day) results from the higher rate of observed weight gain in inpatient settings (around 10–20 g/kg per day) compared to community settings (around 5 g/kg per day).[7] A dosage proportional to weight presents a paradox in which children receive more RUTF when they are nearer recovery than at the more life-threatening stage at the start of treatment. Studies show that weight and MUAC gain are maximal in the first 2–3 weeks of supplementation and slower in children with higher absolute weight when provided the same ration.[8–10] A study of lean tissue mass accretion in children classified with moderate acute malnutrition show acceptable rates of weight and MUAC gain where more than 90% of gain is attributable to fat-free mass while receiving 500 kcal per day, approximately 50–75 kcal/kg/day.[11] This suggests that it is feasible to reduce the daily ration amount once a child who presents with SAM has recovered into the MAM category. As RUTF and health-care staff salaries are major cost drivers of Community-based Management of Acute Malnutrition (CMAM) programmes, strategies that use less RUTF per child and reduce time demands on health-care staff may improve access to care.

Moreover, the current distinction between severe and moderate acute malnutrition has resulted in separate programmes overseen by different United Nations agencies using different protocols and products: RUTF or ready-to-use supplementary food (RUSF) or fortified-blended flours for children with severe or moderate acute malnutrition, respectively. This complicates case detection, delivery of care and supply-chain

management.[12] RUTF and RUSF are similar in most regards except for protein source, with RUTF using milk and RUSF either refined soy or a combination of refined soy and milk. RUSF was initially developed to reduce costs. RUTF has proven to be effective in promoting rapid weight gain and rehabilitation even in children with moderate acute malnutrition.[13–16] Combining severe and moderate acute malnutrition treatment into a single programme, and adjusting RUTF dosage as children respond to treatment, could optimise cost allocation and simplify programme management, thereby increasing overall effectiveness.[13,14,17]

We conducted an individually randomised controlled trial in the Democratic Republic of the Congo (DRC) in children aged 6–59 months with uncomplicated acute malnutrition. In children with MUAC less than 125 mm or with oedema at baseline, we found that gradually decreasing RUTF dosage while weight and MUAC increased was superior to the current DRC standard protocol in terms of nutritional status (including relapses as failure) at 6 months post-inclusion.[18] No study with a randomised controlled design compared such a strategy specifically in children with severe acute malnutrition, and only one analysed a RUTF reduced dosage in comparison with the standard RUTF dosage in a relatively food secure context in Burkina-Faso.[19]

We hypothesised that the OptiMA strategy would be non-inferior to the current DRC national CMAM protocol in children 6–59 months old with uncomplicated severe acute malnutrition.

Methods

Study design and participants

The OptiMA-DRC trial was a two-arm, open-label, individually randomised controlled non-inferiority trial conducted in the Kamuesha health zone, Kasai Province, DRC.[20] Kamuesha is a remote district with a population of 500,000, 26 health centres and one district hospital. In 2018, this landlocked, rural health zone had just experienced 2 years of armed conflict with significant population displacement and emergency levels of food insecurity.[21] Prevalence of severe acute malnutrition was estimated at 11.8% based on MUAC and 3.1% based on WHZ score or oedema.[22] The trial was nested within a nutritional project launched May 1, 2018 by the non-governmental organisation The Alliance for International Medical Action (ALIMA), in collaboration with the Congolese Ministry of Health, to implement the national protocol for severe acute malnutrition treatment for the first time[23] and support paediatric care in nine health centres and the district hospital.

The study was conducted in four health centres (selected based on demographic, epidemiological, and logistical factors) covering 12,000 children aged 6–59 months spread over 60 villages. Eligible children were identified by trained nurses helped by trained community health workers through monthly malnutrition screenings in all villages or among children presenting for consultations at any of the four health centres. MUAC, WHZ score and presence of oedema were used to identify children with severe acute malnutrition for whom an inclusion visit at the relevant health centre was proposed.

All children living in the catchment area aged 6–59 months with a MUAC less than 115 mm or WHZ score less than −3 or nutritional oedema grade 1 or 2 were eligible. Children were excluded if they had medical conditions requiring hospitalisation; no appetite; grade 3 nutritional oedema; known allergy to milk, peanuts, or RUTF; any chronic pathology; MUAC of 125 mm or larger with no nutritional oedema and a WHZ score of less than −3; or siblings of children already in the trial. Among excluded children, those with MUAC of 125 mm or larger and no oedema but a WHZ score of less than −3 received standard treatment, and those who had a sibling already randomly assigned received the same treatment as their sibling, all were not included in the analysis.

Children were enrolled after caregivers gave written informed consent. Ethical approval with annual renewal was granted by the DRC National Ethics Committee (approval number 94/CNES/BN/PMMF/2018) and the Ethics Evaluation Committee of the French National Institute for Health and Medical Research (INSERM, approval number 18–545).

Randomisation and masking

Children were randomly assigned 1:1 to the OptiMA group (intervention) or the standard group (in reference to the national CMAM protocol).[23] Randomisation was performed using specially developed software uploaded onto tablets that hosted the randomisation lists prepared in advance by an independent statistician and which were inaccessible to trial staff. After verifying eligibility, the study nurse ran the randomisation software which assigned a code and corresponding treatment arm. Trial and clinic staff were unmasked as to treatment assignment. Confidential randomisation blocks were used, stratified by trial centre and WHO category of severe or moderate acute malnutrition.

Procedures

In the OptiMA group, children received a RUTF dosage that decreased as the child's weight and MUAC increased. The theoretical based dosage was 175 kcal/kg/day, 125 kcal/kg/day and 75 kcal/kg/day of RUTF for children with MUAC <115 mm or oedema, with MUAC 115–119 mm and with MUAC ≥120 mm, respectively. The OptiMA RUTF dosage table uses 500 gr increments to calculate the weekly ration provided to the child. The formula applied for the calculation of the weekly ration prescribed was weight in kg*RUTF dosage intake according to MUAC category (Kcal/kg/day)*7

days/500 Kcal (i.e., one sachet of RUTF). Each result was then rounded up to the above whole number. Following this calculation, the final dosage provided was 170–200 kcal/kg per day for children with MUAC of less than 115 mm, 125–190 kcal/kg per day for those with MUAC between 115 mm and 119 mm, and 50–166 kcal/kg per day for children with a MUAC of 120 mm or larger (Appendix 2 p 1). Children with oedema and MUAC of 115 mm or larger received the same RUTF dose as those with MUAC of less than 115 mm until the oedema resolved, and thereafter received the dosage for children with MUAC of 115 mm or larger (Appendix 2 p12). Children in the standard group received an amount of RUTF that increased as the child's weight increased (weight bands ranging from 1.5 kg to 2 kg increments) at a dosage of 150–200 kcal/kg per day (Appendix 2 p 1).

According to the DRC national CMAM protocol,[24] children received RUTF until reaching a MUAC of 125 mm or larger or a WHZ score of –1.5 or higher without oedema for two consecutive weeks and afterwards, a nutritional support with RUSF for 3 months (Appendix 2 p 1). According to the OptiMA strategy, children receive RUTF until reaching a MUAC of 125 mm or larger without oedema for two consecutive weeks (Appendix 2 p 1). In both groups, a one-week ration of RUTF was distributed at the visit when recovery was determined. RUTF stock and delivery were managed by ALIMA. RUSF stock and delivery were managed by another Ministry of Health partner in charge of the program managing moderate cases.

Children in both groups were monitored for 6 months from inclusion. Children were asked to visit the trial centre once a week (once a fortnight for those living more than 14 km) while receiving RUTF. At each visit, collected data included: MUAC and weight; amount of RUTF provided; results from any rapid diagnostic test for malaria; and whether any clinical symptoms were present. Children were referred to hospital as indicated. Height was measured once a month. After discharge from RUTF treatment (or due to a missed health centre visit), children received fortnightly follow-up home visits until 6 months' post-inclusion where a nurse assisted by community health workers collected the following data: MUAC and weight; results from any rapid diagnostic test for malaria; and whether any clinical symptoms were present. Any child who needed nutritional or medical care was referred to the trial centre or the Kamuesha general hospital. Height was measured once a month.

All children received amoxicillin 50–100 mg/kg per day for 7 days, vitamin A and an anthelmintic, as well as a rapid malaria test at inclusion (and at follow-up visits for children with malaria symptoms); if positive, an artemisinin-based combination therapy was prescribed. Children were managed by Ministry of Health personnel according to the DRC national CMAM protocol[23] in all aspects of care except for RUTF dosage and anthropometric criteria for beginning and ending RUTF treatment for children in the OptiMA group.

Outcomes

Recovery, measured throughout the 6-month follow-up period, was a composite variable meeting all of the following for two consecutive weeks after receiving treatment for at least 4 weeks: axillary temperature below 37.5 °C; absence of nutritional oedema; and anthropometric recovery. In the primary analysis, anthropometric recovery corresponded to the criteria specific to each strategy: a MUAC of 125 mm or larger or WHZ score of –1.5 or higher as per the DRC national CMAM protocol in the standard group, and MUAC of 125 mm or larger with no reference to WHZ score in the OptiMA group. We use the programmatic criteria for ending RUTF treatment according to each strategy. We hypothesised that this might impact the proportion of children reaching recovery and have consequences on nutritional status at the recovery visit, so we compared, in sensitivity analyses, recovery proportion, RUTF treatment amount and duration and anthropometrics parameters in both groups by applying the anthropometric criteria for ceasing nutritional treatment specific to each strategy.

Secondary endpoints were MUAC, WHZ score, weight-for-age z score (WAZ score) and height-for-age z score (HAZ score) calculated at 6 months; total weight, MUAC and height gain; hospitalisation proportion; overall amount and cost of RUTF and RUSF provided; and time to recovery between inclusion and 6 months. We plotted, post-hoc, anthropometric changes by study arm over the 6-month follow-up period by fitting curves on the mean of MUAC, WAZ score, WHZ score and curves on the mean of MUAC, weight and height accumulated. We compared nutritional status at 6 months through a composite variable that took into account vital status, acute malnutrition status, and whether there was relapse into severe or moderate acute malnutrition according to WHO definitions. Relapse into moderate acute malnutrition was defined as a MUAC between 115 and 124 mm or a WHZ score between –3 and –2 after the child was free of acute malnutrition (i.e., MUAC of 125 mm or larger and WHZ score of –2 or higher and no oedema) at a previous visit. We distinguished children with relapse into moderate acute malnutrition still ongoing at 6 months ('relapse unresolved') and those who recovered from this new episode ('relapse resolved'). Relapse into severe acute malnutrition was defined as a MUAC less than 115 mm or a WHZ score less than –3 or oedema after the child was free of acute malnutrition at a previous visit or after the child relapsed into moderate acute malnutrition and afterwards met the criteria of severe acute malnutrition. We also compared between arms the median time for being free from acute malnutrition according to WHO definition in children with a complete 6-month trial follow-up.

Among children who recovered during follow-up, we presented anthropometric parameters at the visit when children fulfilled the strict definition of recovery. We also calculated indicators that are typically reported by CMAM programs[24]: daily weight gain velocity (g/kg per day), weekly MUAC gain (mm per week), quantity of RUTF distributed and length of RUTF treatment between inclusion and recovery visit, and recovery proportion at 12 and 16 weeks (which are routinely used as maximum length of follow-up).

Statistical analysis

This was a non-inferiority analysis comparing the OptiMA and standard groups in terms of recovery proportions over 6 months in the intention-to-treat (ITT) and per-protocol (PP) populations. ITT included all participants. PP analysis included those who were prescribed RUTF for at least 4 weeks, received at least 90% of the total amount of RUTF they were due as per the protocol (Appendix 2 p 2), and had a maximum interval of 6 weeks between any two visits during follow-up. OptiMA was to be considered as non-inferior to the standard if the upper bound of the 95% confidence interval (CI) for the difference in the proportion of recovery between groups was lower than 10% in both ITT and PP analyses. Assuming an 85% proportion of recovery in the standard group and a one-side type-I error of 2.5%, we calculated that 414 participants would provide 80% power to demonstrate non-inferiority of the OptiMA strategy. The sample size was set at 476 participants to account for 15% loss-to-follow-up.

For secondary endpoints, we performed superiority analysis using Student's t test or Wilcoxon's test and χ^2 or Fisher's exact tests. We also did a Kaplan-Meir time-to-event analysis and log-rank test to compare the probability of recovery over time. We used mixed-effects generalised additive models for fitting and plotting means of anthropometric parameters. The smooth terms in the model were represented by using penalised regression splines. Covariates included the randomisation treatment, interaction terms between randomisation treatment and time, adjusted for child's age at each visit. The mixed effects models used hierarchical random effects for individuals (intercept and slope for linear time in each model) to account for the correlation at each level when estimating the variance. We represented a 95% confidence interval band around each curve to compare randomisation groups. These secondary analyses were post-hoc and done in the overall populations and among five sub-groups of participants with different vulnerable anthropometric criteria at inclusion: children with bipedal oedema (sub-group 1), MUAC of less than <110 mm (sub-group 2), MUAC of less than 115 mm and WHZ score of less than −3 (subgroup 3), MUAC of less than 115 and WHZ score of −3 or larger (subgroup 4), WHZ score of less than −3 and MUAC of 115 or larger (sub-group 5). We assumed the reduction of RUTF dosage in these particular children could impair nutritional rehabilitation. For each secondary analysis, a p-value of less than 0.05 was considered significant. All analyses were done with R software and packages, version 4.1.2.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study. R.B. and S.S. had final responsibility for the decision to submit the manuscript for publication.

Results

Participants and follow-up

Between July 22, 2019 and January 20, 2020, 491 children were randomised, of whom 9 (2%) were excluded and 482 (98%) were included for analysis (240 in the standard group and 242 in the OptiMA group; Fig. 1). Baseline, sociodemographic, anthropometric and clinical characteristics were similar in both groups (Table 1). During follow-up (Table 2), 2 children died (one in each group), 2 were lost to follow-up (one in each group), 18 moved out of the study area with their families (6 in the standard group and 12 in the OptiMA group) and 460 completed the 6-month follow-up (232 *vs* 228). Overall, 55 children were hospitalised at least once (28 *vs* 27), with malaria or respiratory infection the main diagnosis at first hospitalisation (21 *vs* 18) (Table 2).

Primary endpoint

In the ITT analysis, 234 (98%) children in the standard group and 231 (96%) children in the OptiMA group recovered (difference 2.0%, 95% CI −2.0 to 6.4; Table 3). In the PP analysis, 230 (98%) children in the standard group and 228 (97%) children in the OptiMA group recovered (difference 1.3%, 95% CI −2.3 to 5.1). Sensitivity analyses showed similar results in ITT and PP analysis when either the standard recovery definition was applied to each group (difference 0.8%, 95% CI −3.0 to 4.8 in ITT; difference 0.0%, 95% CI −2.2 to 5.1 in PP; Appendix 2 p 3) and when the OptiMA recovery definition was applied to each group (difference −1.3%, 95% CI −7.3 to 1.9 in ITT; difference −2.1%, 95% CI −6.8 to 2.1 in PP) (Appendix 2 p 4).

Time to recover and secondary outcomes among recovered children

Median time to recovery was 4 weeks in the standard group (IQR 4–7) and 6 weeks in OptiMA (IQR 4–9) ($p < 0.0001$; Appendix 2 p 5) when using the trial definition of recovery specific to each group. Among the 234 children who recovered in the standard group, 71 children (30%) had a MUAC of less than 125 mm, meaning they were classified as recovered by achieving a WHZ

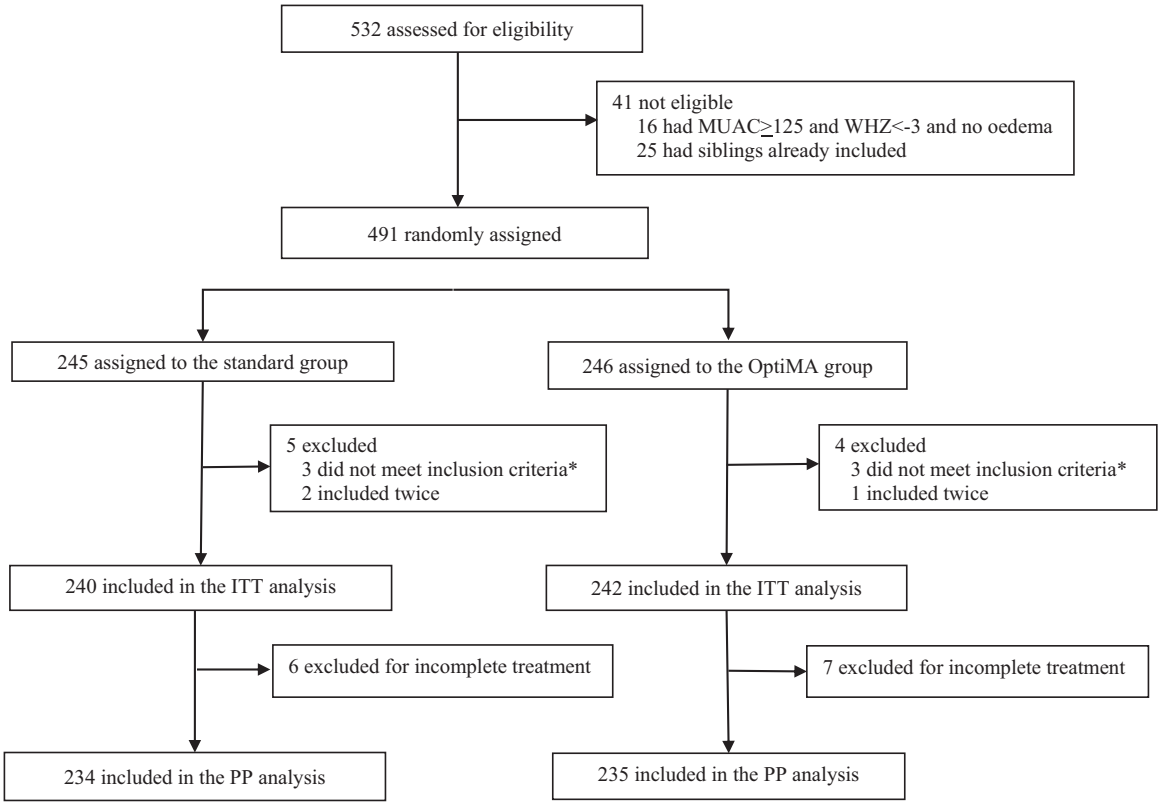

Fig. 1: **Trial flow chart.** ITT = intention-to-treat. MUAC = mid-upper-arm circumference. PP = per-protocol. WHZ = weight-for-height z score. *Five children had a mid-upper-arm circumference of 125 mm or larger and a weight for height z score less than −3 and no oedema at inclusion (2 standard and 3 OptiMA) and one child in the standard group had a mid-upper-arm circumference of 115 mm or larger and a weight for height z score of −3 or more and no oedema.

of −1.5 or larger but still had acute malnutrition according to MUAC (Appendix 2 p 5). When the same anthropometric recovery definition was applied to each group (i.e., either the standard or the OptiMA definition) in sensitivity analyses, there was no difference between groups in terms of time to recovery, recovery proportion by weeks 12 and 16, and anthropometric parameters at the recovery visit (Appendix 2 p 5–6).

Evolution of anthropometric parameters over follow-up period and nutritional status at 6 months post-inclusion

Growth curves in both groups (Fig. 2, Appendix 2 p 9–12) were similar for all parameters over the 6-month follow-up among the overall population and among all subgroups. The 95% confidence interval bands of both arms overlapped from inclusion to month 6 in all subgroups, except subgroup 5 (children with WHZ score of less than −3 and MUAC of 115 or larger), for whom we observed a higher cumulative weight gain curve in favour of the standard group (Appendix 2 p 12).

At 6 months, 87 children relapsed into moderate acute malnutrition in the standard group compared to 51 in the OptiMA group after being free of acute malnutrition at a prior visit, while 25 children overall relapsed into severe acute malnutrition (12 *vs* 13; Table 2). Among children who relapsed into moderate acute malnutrition, 43 were still affected at month 6 (32 *vs* 11), in line with the higher proportion of children presenting a MUAC of less than 125 mm in the standard arm (15% *vs* 5%; p = 0.0004; Table 2). The median time to be free from acute malnutrition according to the WHO definition for at least at one visit was 5 weeks in both arms (Table 2). Secondary outcomes in both arms were similar in subgroups 1 (bipedal oedema, Table 2) and 5 (WHZ score less than −3 and MUAC of 115 or larger, Appendix 2 p 15). Among subgroups 2 (MUAC less than 110 mm, Table 2), 3 (MUAC less than 115 mm and WHZ score less than −3) and 4 (MUAC less than 115 and WHZ of −3 or higher) (Appendix 2 p 13–14), median total weight gain from inclusion was higher in the OptiMA arm, and the proportion of children relapsing into moderate acute malnutrition and the proportion of children with MUAC of less than 125 mm were lower in the OptiMA arm.

	Standard group (n = 240)	OptiMA group (n = 242)
Sociodemographic characteristics		
Sex		
Male	124 (52%)	119 (49%)
Female	116 (48%)	123 (51%)
Age, months		
Median (IQR)	17 (10–30)	16 (9–29)
6–24	148 (62%)	151 (62%)
Currently breastfed	151 (63%)	160 (66%)
Number of siblings	3 (1–4)	3 (1–5)
Birth order	3 (2–5)	3 (2–5)
First-born child	42 (18%)	40 (17%)
Caretaker was illiterate	200 (83%)	202 (83%)
Mother as caretaker	197 (82%)	199 (82%)
Maternal age[a], year	26 (20–32)	27 (22–31)
Number of birth per mother	4 (2–6)	4 (2–6)
Health centre's distance from the village >14 km	30 (12%)	31 (13%)
Anthropometric characteristics		
Weight, kg	7.0 (5.9–8.5)	7.0 (5.8–8.4)
Height, cm	71.5 (65.5–79.1)	71.2 (65.5–78.3)
Nutritional oedema	49 (20%)	38 (16%)
MUAC, mm		
Median (IQR)	114 (110–121)	114 (111–120)
<110	37 (15%)	29 (12%)
<115	144 (60%)	148 (61%)
[115–124]	96 (40%)	94 (39%)
MUAC <115 mm and WHZ score <−3	47 (20%)	48 (20%)
MUAC <115 mm and WHZ score ≥−3	97 (40%)	100 (41%)
MUAC ≥115 mm and WHZ score <−3	52 (22%)	62 (26%)
WHZ score[b]	−2.7 (−3.3 to −2.0)	−2.6 (−3.2 to −2.0)
<−3	75 (39%)	72 (35%)
<−2	145 (76%)	152 (75%)
WAZ score[b]	−3.7 (−4.1 to −3.1)	−3.5 (−4.2 to −2.9)
<−3	145 (76%)	140 (69%)
<−2	182 (95%)	194 (95%)
HAZ score	−3.0 (−4.0 to −1.9)	−2.9 (−3.9 to −1.9)
<−3	113 (47%)	113 (47%)
<−2	172 (72%)	171 (71%)
Medical and nutritional characteristics		
Temperature axillary >37.4 °C	16 (7%)	21 (9%)
Had a malaria rapid antigen test	227 (95%)	232 (96%)
Malaria rapid antigen test positive	124/227 (55%)	129/232 (56%)
ACT received	116/124 (94%)	114/129 (88%)
Diarrhoea	7 (3%)	7 (3%)
Respiratory infection	1 (0%)	1 (1%)
RUTF treatment initiated	240 (100%)	242 (100%)
Amoxicillin received	240 (100%)	242 (100%)
Subgroup 1: Children with nutritional oedema	**Standard group (n = 49)**	**OptiMA group (n = 38)**
Female	22 (45%)	18 (47%)
Age, month	26 (15–36)	25 (15–42)
Weight, kg	8.8 (7.3–10.3)	8.9 (7.5–10.4)
Height, cm	79.0 (71.1–84.0)	77.2 (72.0–87.0)
MUAC, mm	123 (122–124)	124 (122–127)
Nutritional oedema grade 1	43 (88%)	34 (89%)
Nutritional oedema grade 2	6 (12%)	4 (11%)

(Table 1 continues on next page)

Subgroup 2: Children with a MUAC <110 mm	Standard group (n = 37)	OptiMA group (n = 29)
(Continued from previous page)		
Female	19 (51%)	18 (62%)
Age, month	10 (8–24)	10 (7–24)
Weight, kg	5.8 (5.1–6.7)	5.8 (5.0–7.1)
Height, cm	65.5 (62.7–72.0)	66.5 (60.5–72.0)
MUAC, mm	105 (104–106)	105 (102–106)
Nutritional oedema grade 1	0 (0%)	1 (3%)
WHZ score <−3	3 (8%)	1 (3%)

Data are n (%), n/N (%), or median (IQR). ACT = Artemisinin-based combination therapy. HAZ = height-for-age z score. MUAC = mid-upper-arm circumference. RUTF = ready to use therapeutic food. WAZ = weight-for-age z score. WHZ = weight for-height z score. [a]The calculation excludes 1 deceased mother and 1 missing data. [b]The calculation excludes children with nutritional oedema.

Table 1: **Baseline characteristics.**

	Standard group (n = 240)	OptiMA group (n = 242)	p
Characteristics of follow-up			
Children has completed the 6 month follow-up	232 (97%)	228 (94%)	0.57
Family moved out of study area	6 (3%)	12 (5%)	
Lost to follow-up	1 (<1%)	1 (<1%)	
Death	1 (1%)	1 (<1%)	
Number visits at the trial centre and at home[a]	15 (13–16)	14 (13–16)	0.41
Number of visits at the trial centre	6 (4–9)	6 (4–8)	0.54
Interval between two visits at the trial centre, days	7 (7–7)	7 (7–7)	
Number of home visits	8 (6–10)	8 (6–9)	0.31
Albendazole received	232 (97%)	232 (96%)	0.63
Vitamin A supplementation received	238 (99%)	238 (98%)	1.00
Caretaker trained to MUAC bracelet use	236 (98%)	238 (98%)	1.00
Amount of RUTF distributed[b], sachet	147 (119–210)	78 (60–120)	<0.0001
RUTF treatment duration, days	49 (42–77)	49 (35–77)	0.39
Amount of RUSF distributed, sachet	0	0	
Vital and nutritional status at 6 months[c]			0.020
Children alive without AM nor relapse	135 (56%)	156 (65%)	
Relapsed into MAM, resolved at Month 6	45 (19%)	40 (17%)	
Relapsed into MAM, unresolved at Month 6	32 (13%)	11 (5%)	
Relapsed into SAM	12 (5%)	13 (5%)	
AM from inclusion to Month 6	8 (3%)	8 (3%)	
Discontinued trial	7 (3%)	13 (5%)	
Death	1 (<1%)	1 (<1%)	
Time for being free of AM since inclusion, days (n = 444)[f]	44 (21–56)	38 (28–58)	0.26
Anthropometric parameters[d]			
Weight, kg	9.0 (7.8–10.8)	9.0 (8.0–10.7)	0.68
Height, cm	73.8 (67.5–81.0)	73.6 (68.0–80.5)	0.90
MUAC, mm	131 (126–136)	131 (128–136)	0.11
<115 mm	4 (2%)	5 (2%)	1.00
<125 mm	36 (15%)	12 (5%)	0.0004
WHZ score	−0.3 (−1.1 to 0.7)	0.0 (−0.9 to 0.8)	0.075
<−3	3 (1%)	2 (1%)	0.68
<−2	23 (10%)	16 (7%)	0.30

(Table 2 continues on next page)

	Standard group (n = 240)	OptiMA group (n = 242)	p
(Continued from previous page)			
HAZ score	−3.9 (−5.0 to −3.0)	−3.8 (−4.9 to −2.8)	0.28
<−3	177 (76%)	173 (72%)	0.39
<−2	213 (91%)	214 (89%)	0.50
WAZ score	−2.3 (−3.2 to −1.5)	−2.0 (−2.9 to −1.4)	0.094
<−3	69 (30%)	53 (22%)	0.083
<−2	142 (61%)	123 (51%)	0.042
Change in anthropometric parameters[d]			
Weight gain, g	2000 (1300–2700)	2100 (1500–2700)	0.075
MUAC gain, mm	16 (12–20)	17 (13–21)	0.13
Height gain, cm	1.9 (1.3–2.9)	1.9 (1.4–2.8)	0.59
Hospitalisation			
Children with at least one follow-up visit with indication for reference to hospital	45 (19%)	48 (20%)	0.85
Main indication for hospitalisation: stagnant or weight loss	33 (73%)	31 (64%)	0.73
Children hospitalised at least once	28 (12%)	27 (11%)	0.97
Main diagnosis[e]			0.54
Malaria or respiratory infection	21/28 (75%)	18/27 (67%)	
Stagnant or weight loss	4/28 (14%)	3/27 (11%)	
Diarrhoea or deshydratation	1/28 (4%)	4/27 (15%)	
Others	1/28 (4%)	2/7 (7%)	
Vital prognosis engaged	1/28 (4%)	0/27 (0%)	
MUAC[e], mm	110 (105–115)	110 (105–114)	0.55
80 ≤ MUAC < 111	16 (57%)	16 (59%)	1.00
111 ≤ MUAC < 140	12 (43%)	11 (41%)	
Nutritional oedema[e]	2 (7%)	1 (4%)	0.49
Length of therapeutic milk F75 received[e], days	3 (2–4)	2 (2–3)	0.22
Length of therapeutic milk F100 received[e], days	1 (1–3)	2 (2–2)	0.64
Length of RUTF received[e], days	6 (4–8)	6 (4–8)	0.89
MUAC at the end of hospitalisation[e], mm	115 (108–120)	112 (108–119)	0.84
Length of hospitalisation[e], days	5 (3–6)	5 (3–5)	0.49

Subgroup 1: Children with nutritional oedema at baseline	Standard group (n = 49)	OptiMA group (n = 38)	p
Children hospitalised at least once	3 (6%)	1 (3%)	0.63
Main diagnosis: malaria or respiratory infection	3/3 (100%)	1/1 (100%)	
Weight, kg	10.2 (8.5–11.6)	10.7 (9.0–11.6)	0.63
Height, cm	80.6 (74.2–86.2)	78.4 (73.9–88.7)	0.93
MUAC, mm	134 (128–140)	135 (129–140)	0.56
<125 mm	4 (8%)	0 (0%)	0.20
WHZ score	−0.5 (−1.3 to 0.7)	−0.4 (−1.3 to 0.6)	0.89
WAZ score	−2.1 (−2.8 to −1.2)	−2.1 (−3.0 to −1.4)	0.83
HAZ score	−3.3 (−4.1 to −2.7)	−3.5 (−4.7 to −2.2)	0.96
MUAC gain, mm	12 (6–17)	11 (6–17)	0.97
Weight gain, g	1400 (900–2200)	1500 (1000–1800)	0.97
Height gain, cm	1.5 (1.1–2.1)	1.4 (1.0–2.0)	0.50
Vital and nutritional status at 6 months[c]			0.84
Children alive without AM nor relapse	31 (63%)	25 (66%)	
Relapsed into MAM, resolved at Month 6	7 (14%)	4 (11%)	
Relapsed into MAM, unresolved at Month 6	7 (14%)	4 (11%)	
Relapsed into SAM	2 (4%)	1 (3%)	
AM from inclusion to Month 6	1 (2%)	1 (3%)	
Discontinued trial	1 (2%)	3 (8%)	
Time for being free of AM since inclusion, days (n = 81)[f]	21 (14–28)	21 (14–33)	0.80
Amount of RUTF distributed, sachet	140 (112–147)	68 (62–82)	<0.0001
RUTF treatment duration, days	35 (35–49)	35 (35–42)	0.14

(Table 2 continues on next page)

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Subgroup 2: Children with MUAC <110 mm at baseline	Standard group (n = 37)	OptiMA group (n = 29)	p
Hospitalised, at least once	10 (27%)	7 (24%)	0.92
Main diagnosis: malaria or respiratory infection	8/10 (80%)	5/7 (71%)	
Weight, kg	7.9 (6.9–8.6)	7.9 (7.5–9.5)	0.20
Height, cm	68.5 (64.4–74.2)	70.4 (65.2–74.0)	0.46
MUAC, mm	124 (120–130)	128 (125–131)	0.14
<125 mm	19 (51%)	5 (17%)	0.0093
WHZ score	−0.7 (−1.8 to 0.6)	0.3 (−0.7 to 1.0)	0.16
WAZ score	2.7 (−3.8 to −2.0)	−2.2 (−3.2 to −1.5)	0.046
HAZ score	−4.5 (−5.8 to −3.6)	−4.0 (−4.9 to −3.3)	0.135
Total MUAC gain, mm	20 (15–25)	24 (21–28)	0.042
Total weight gain, kg	1900 (1300–2700)	2600 (2200–3000)	0.0060
Total height gain, cm	1.9 (1.0–3.0)	2.7 (1.7–4.0)	0.074
Vital and nutritional status at 6 months[c]			0.019
Children alive without AM nor relapse	11 (30%)	20 (69%)	
Relapsed into MAM, resolved at Month 6	8 (22%)	2 (7%)	
Relapsed into MAM, unresolved at Month 6	9 (24%)	1 (3%)	
Relapsed into SAM	3 (8%)	2 (7%)	
AM from inclusion to Month 6	4 (11%)	3 (10%)	
Discontinued trial	2 (5%)	1 (3%)	
Death	0 (0%)	0 (0%)	
Time for being free of AM since inclusion, days (n = 56)[f]	70 (49–81)	65 (42–87)	0.91
Amount of RUTF distributed, sachet	182 (147–245)	143 (84–173)	0.0017
RUTF treatment duration, days	77 (63–98)	77 (56–105)	0.90

Data are n (%), n/N (%), or median (IQR). AM = acute malnutrition. cm = centimeter. g = gramme. HAZ = height-for-height z score. kg = kilogramme. MAM = moderate acute malnutrition. Mm = millimeter. MUAC = mid-upper-arm circumference. RUSF = ready to use supplemented food. RUTF = ready to use therapeutic food. SAM = severe acute malnutrition. WAZ = weight-for-age z score. WHZ = weight for-height z score entered by health caretakers. [a]Standard group: 3626 follow-up visits of which 1805 home visits, 1767-programmed follow-up visits at research site, and 54 spontaneous paediatric outpatient visits at research site; OptiMA group: 3522 follow-up visits of which 1761 home visits, 1710-programmed follow-up visits at research site and 51 spontaneous paediatric outpatient visits at research site. [b]Standard group: 42,896 sachets (286 boxes) distributed corresponding to 12,012 US dollar costs; OptiMA group: 23,267 sachets (155 boxes) distributed corresponding to 6510 US dollar costs; one box of RUTF costs 42 USD in DRC in 2021. [c]Acute malnutrition refers to the WHO definition: a child presenting a mid-upper-arm circumference less than 125 mm or a weight for height less than −2 or oedema. Relapse into moderate acute malnutrition was defined, according to WHO definition, as a mid-upper-arm circumference between 115 and 124 mm or a weight for-height z score between −3 and −2 after the child did not met the acute malnutrition definition at a previous visit. Relapse into severe acute malnutrition was defined, according to WHO definition, as a mid-upper-arm circumference less than 115 mm or a weight for-height z score less than −3 or oedema after the child did not met the acute malnutrition definition at a previous visit; or after the child relapse to moderate and then to severe acute malnutrition. [d]22 children did not complete the 6-month follow-up period, their anthropometric status at the last visit in the trial was considered. [e]Calculated at first hospitalisation of the 55 children hospitalised at least once (28 in the standard group and 27 in the OptiMA group). [f]Calculated in children with a complete 6-month trial follow-up who reached the absence of acute malnutrition according to WHO definition at least at one visit.

Table 2: **Characteristics at 6 months post-inclusion (intention-to-treat analysis).**

Quantity and cost of RUTF provided

From inclusion to 6 months, the total median amount of RUTF provided was 147 (IQR 119–210) in the standard group and 78 (IQR 60–120) sachets in the OptiMA group (Table 2). This corresponded to a higher overall amount [cost] of RUTF between inclusion and month 6 in the standard arm (42,896 sachets [USD 12,012] *vs* 23,267 sachets [USD 6510]) (footnotes Table 2).

Discussion

In this study of children with uncomplicated severe acute malnutrition in a severely food insecure context of the DRC, the recovery proportion in the group treated with a decreasing RUTF dose was non-inferior to the group treated with the standard RUTF dose. Recovery proportion in ITT and PP was similar between the two strategies either when using their own specific programmatic definitions or when applying the same criteria to both. Secondary endpoints allowed reporting robust secondary efficacy assessment comparable between both groups of children at 6 months. The OptiMA strategy (one program based on MUAC with one nutritional product with a reduced dosage) led to higher weight gain and absolute MUAC value at 6 months with 46% less RUTF distributed overall. We also observed the same trends in the subgroups of children with MUAC less than 110 mm, with MUAC less than 115 mm and WHZ less than −3 or with MUAC less than 115 mm and WHZ less than −3 at baseline. In both the overall population and in vulnerable subgroups, children had generally similar anthropometric changes over 6-months with no difference between groups in terms of hospitalisations and relapses into severe acute malnutrition over the follow-up period.

	Standard group	OptiMA group	Difference (95% CI)
Intention-to-treat analysis			
Number of patients	240	242	
Recovered[a]	234 (98%)	231 (96%)	2.0% (95% CI −2.0% to 6.4%)
MUAC < 125 mm	0 (0%)	3 (1%)	
MUAC <125 mm and WHZ score <−1.5	3 (1%)	0 (0%)	
Recovered one visit only	0 (0%)	1 (<1%)	
RUTF less than 28 days	0 (0%)	1 (<1%)	
Discontinued trial[b]	3 (1%)	5 (2%)	
Death	0 (0%)	1 (<1%)	
Per-protocol analysis[c]			
Number of patients	234	235	
Recovered[a]	230 (98%)	228 (97%)	1.3% (95% CI −2.3% to 5.1%)
MUAC < 125 mm	0 (0%)	5 (2%)	
MUAC <125 mm and WHZ <−1.5	4 (2%)	0 (0%)	
Recovered one visit only	0 (0%)	1 (<1%)	
Death	0 (0%)	1 (<1%)	

Data are n (%), unless stated otherwise. MUAC = mid-upper-arm circumference. WHZ = weight for-height z score. [a]Assessed over the 6 months follow-up trial period: after a 4-week minimum duration of ready-to-use therapeutic food treatment, an axillary temperature less than 37.5 °C, an absence of bipedal edema and a MUAC of 125 mm or larger for the OptiMA arm or a MUAC of 125 mm or larger or a weight-for-height z score of −1.5 or more for the standard arm, for two consecutive weeks. [b]Family moved out of study area and lost to follow-up. [c]Per-protocol definition: minimum prescription of 4 weeks of ready-to-use therapeutic food, children received at least 90% of the total amount of ready-to-use therapeutic food they were supposed to receive as per protocol (Appendix 2 p 2) and a maximum interval of 6 weeks between any two visits in the 6-month follow-up.

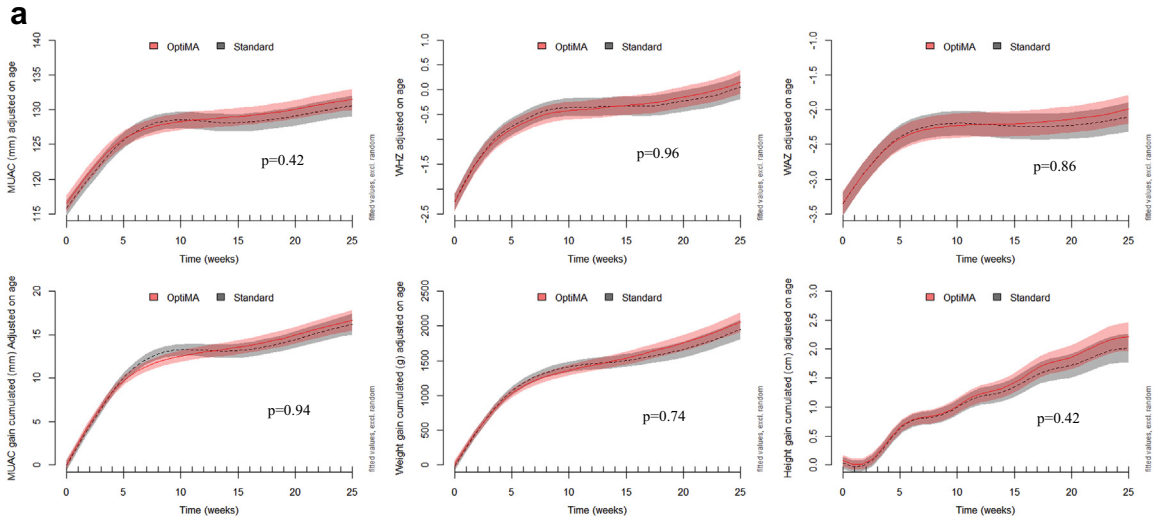
Table 3: **Recovery over 6 months (main endpoint).**

The recovery proportion was higher in each group when compared to those reported elsewhere.[19,25] But such comparisons should be done with caution due to variations in the programmatic definition of recovery specific to countries and studies. In our study, we implemented systematic home visits in case of absences during treatment that allowed us to capture recovery status at home regardless of compliance to planned visits at the health centre.

Our findings are consistent with other studies. An individual randomised controlled trial in a food secure context in Burkina Faso found that weight gain velocity was non-inferior among children with uncomplicated severe acute malnutrition receiving either a reduced or standard RUTF dosage.[19] Both groups had similar recovery proportions at 16 weeks. In line with our secondary results, they found that MUAC gain velocity mirrored weight gain velocity in both groups. A retrospective cohort study comparing reduced and standard RUTF dosage in Sierra Leone reported non-inferiority in terms of MUAC status at 4 weeks. Secondary results showed similar recovery proportions, and similar MUAC and weight gain velocity between groups during RUTF treatment.[25] Both studies reported a small but significant negative effect on linear growth with reduced RUTF dosage, while we found similar height gain in both groups between inclusion and 6 months.

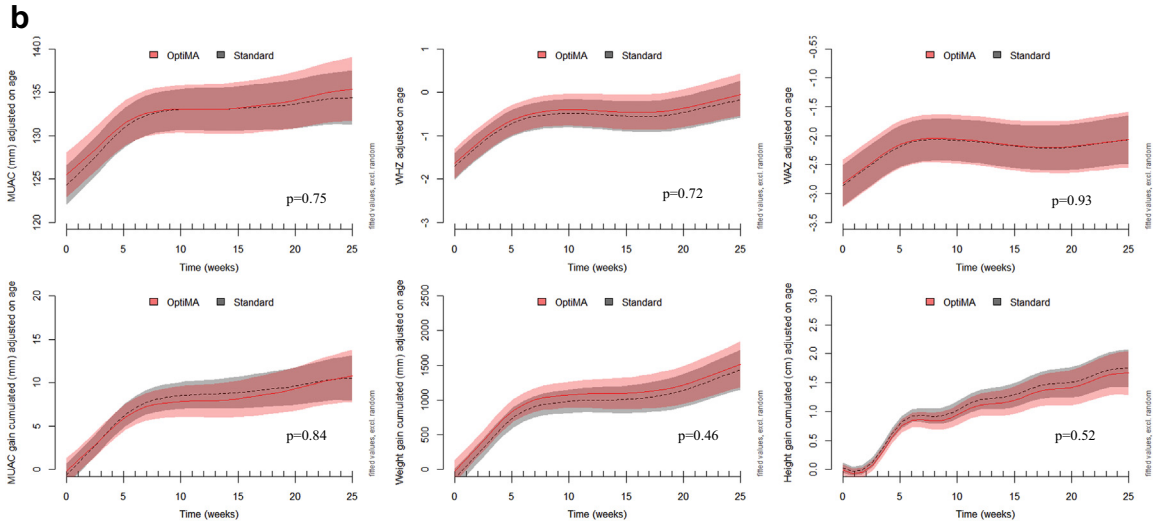
Our study has several strengths. Despite the challenging post-conflict context and landlocked, rural environment, retention and compliance to the trial protocol and to standard care were excellent. We observed a very low lost-to-follow-up rate, probably due to regular home visits. The individually randomised design allowed for robust results, and sensitivity analyses confirmed non-inferiority of OptiMA even when the standard recovery definition was applied to children in the OptiMA group. The fortnightly home follow-up after treatment allowed for close monitoring of anthropometric evolution over 6 months and identifying post-treatment relapses over about 4 months.

This trial not only compared two RUTF dosing protocols but also two programmatic strategies for determining when to begin and end RUTF treatment. It was important to compare current practice in DRC to OptiMA, which dictated applying two different definitions for anthropometric recovery: MUAC or WHZ score for the standard and MUAC only for OptiMA. We assumed the anthropometric parameters and RUTF treatment duration and amount at the recovery visit could differ according to the anthropometric criteria applied. The sensitivity analyses allowed us to test this assumption, and led to important secondary results. Applying an anthropometric recovery definition based on MUAC led to higher total weight and MUAC gain even with much less RUTF distributed but a longer duration of treatment. Reaching a MUAC above 125 mm for two consecutive weeks could be a better indicator for sustaining nutritional recovery than reaching only a WHZ



Weeks	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total
Standard	240	210	224	200	217	155	167	131	132	129	127	114	103	124	99	85	114	110	90	124	99	107	105	112	107	115	3540
OptiMA	242	212	228	203	217	144	145	133	121	110	111	111	112	111	107	98	85	127	78	118	98	105	115	93	118	100	3442
Total	482	422	452	403	434	299	312	264	253	239	238	225	215	235	206	183	199	237	168	242	197	212	220	205	225	215	6982

Number of observation per week by randomisation group for MUAC, WAZ, WHZ, MUAC, weight and height gain cumulated; Total observation 6982



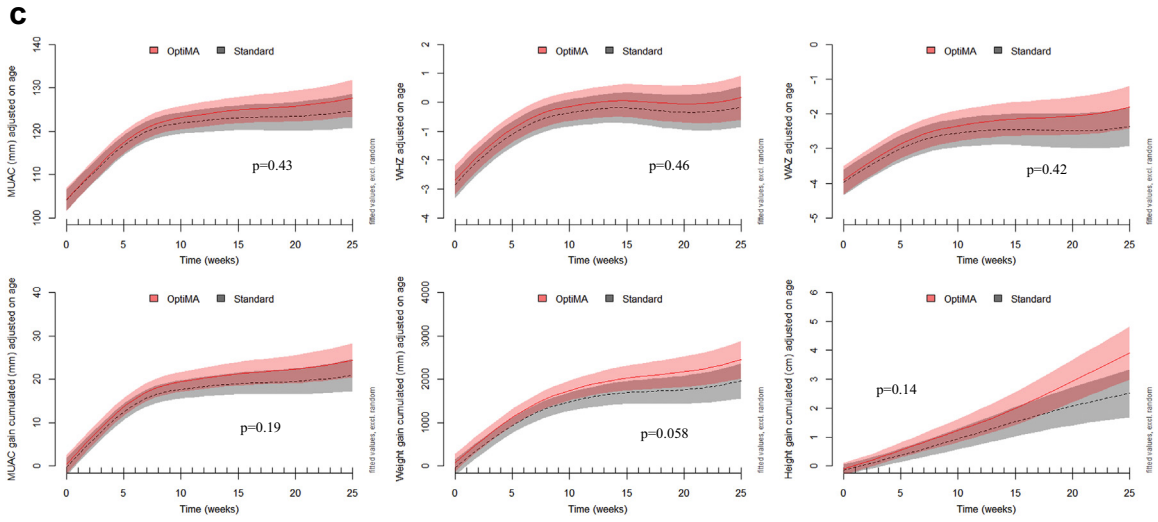
Weeks	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total
Standard	49	47	46	44	44	20	25	22	19	23	24	24	17	29	17	19	17	25	15	31	14	29	17	29	21	31	698
OptiMA	38	38	37	32	36	12	11	22	17	13	14	14	14	18	13	16	11	20	9	15	14	19	10	18	15	19	495
Total	87	85	83	76	80	32	36	44	36	36	38	38	31	47	30	35	28	45	24	46	28	48	27	47	36	50	1193

Number of observation per week by randomisation group for MUAC, WHZ, WAZ, MUAC and weight gain cumulated parameters; Total observation 1193

Fig. 2: **Panel of modelled adjusted weekly means of MUAC, WHZ WAZ and MUAC, weight and height cumulated gain through 6-month by randomisation groups (intention-to-treat).** a: Overall population (n = 482); b: Children with nutritional oedema at baseline (sub-group 1, n = 87); c: Children with MUAC less than 110 mm at baseline (sub-group 2, n = 66). MUAC = mid-upper-arm circumference. WAZ = weight-for-age z score. WHZ = weight for-height z score entered by health caretakers.

score above –1.5. Other studies showing that lower anthropometric measurements, especially MUAC less than 125 mm, at discharge were consistent risk factors for relapse.[26,27]

Comparing relapse rates with other studies may be biased due to differences in definition. A recent systematic review and secondary data analysis of studies that identified relapse up to 18 months post-discharge after standard RUTF treatment found rates ranging from 0% to 37%, with the highest proportions occurring within 6 months of discharge.[28] In our study, the relapse rate into severe acute malnutrition was 5% in both



Weeks	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	Total
Standard	37	26	33	26	31	25	33	26	31	23	23	26	18	19	16	12	19	19	13	15	16	12	17	12	18	13	559
OptiMA	29	22	27	22	22	20	24	21	18	17	19	15	17	13	17	14	10	16	17	18	14	11	13	12	17	10	445
Total	66	48	60	48	53	45	57	47	49	40	42	41	35	32	33	26	29	35	20	33	30	23	30	24	35	23	1004

Number of observation per week by randomisation group for MUAC, WHZ, WAZ, MUAC and weight gain cumulated parameters; Total observation 1004

Fig. 2: Continued

groups, in line with the 4% rate reported in Burkina Faso[19] and 3% in Kenya.[26]

We found more children in the standard group with unresolved new episodes of moderate acute malnutrition at 6 months. None of these children received RUSF supplements because the programme for moderate cases was not functional when they relapsed into moderate acute malnutrition. A similar statistically significant result was shown among the most vulnerable subgroup (children with MUAC less than 110 mm or kwashiorkor at inclusion). This suggests that integrating treatment of moderate and severe acute malnutrition into one programme funded by the same donor, using one product enabled quicker treatment for children who relapsed compared to the standard strategy of two different programmes funded by different donors providing different products. This is a reflection of the current global situation where programmes for treating moderate cases are partially or not functional, resulting in lower coverage compared to treatment programs for severe cases.

RUTF is a major cost driver in malnutrition treatment programmes. At 6 months, children in the OptiMA group had less acute malnutrition (WHO definition) and no relapses with 46% less RUTF distributed overall compared to the standard group (accounting for both initial and relapse episodes). This suggests that OptiMA strategy could confer anthropometric benefits at a lower cost beyond the treatment period.

Our study has some limitations. First, the primary outcome used different anthropometric criteria according to each strategy for ending RUTF treatment. It gives major programmatic information if programmes were to switch to an OptiMA strategy in terms of number of children recovered, time to recover, RUTF consumption but it was not optimal for an efficacy comparison of two treatments. However, the 6-month outcomes and hospitalisation data provided strong evidence of the effectiveness of the OptiMA strategy. Second, children with MUAC of 125 mm or larger and WHZ less than −3 were not eligible for randomisation even though they met the current WHO definition of severe acute malnutrition. But these children only represented 3% (18/532) of the overall population assessed for eligibility, similar to the 2% (117/5075) found in another study in Burkina-Faso.[16] Third, we decided a priori that statistical tests made for the secondary analysis would not be adjusted for multiplicity. Multiple tests might lead to increase in type I error, and should therefore be interpreted with caution. Third, patterns of severe acute malnutrition differ across contexts so it may not be possible to generalise our conclusions. But in this area with emergency levels of severe food insecurity, we found that the reduced dosage was not harmful even for the most severely malnourished children. A 3-arm trial is currently underway in Niger to compare OptiMA with another reduced dosage strategy (ComPAS) and the national standard, which will both test OptiMA in another context and put it in perspective with ComPAS.[29]

In conclusion, this study adds evidence to the safety of treating children with uncomplicated severe acute

malnutrition with a progressively reduced dose of RUTF as their MUAC and weight increase with significant RUTF cost savings. These findings could have substantial individual and public health implications, especially at a time when disruptions caused by COVID-19 may increase the burden of acute malnutrition while reducing treatment coverage.[30]

Contributors

S.S. and R.B. developed the clinical (S.S.) and methodological (R.B.) study concept. R.B., C.C., X.A., D.G., M.D., A.A., K.P. and S.S. designed the study methodology and wrote the protocol. C.C., V.H., H.B., R.A. and M.K. coordinated the study teams. L.I.B., G.T.S., T.S. and B.B.S. coordinated the MoH staff working on the trial. C.C., V.H., H.B., L.I.B., G.T.S., A.K., C.Y. and R.B. organised and supervised data collection. C.Y. created the software tool for randomisation and developed the database. C.C., D.G., X.A., S.S. and R.B. developed the statistical analysis strategy. C.C. performed the statistical analysis and all co-authors interpreted the results. C.C. wrote the first draft of the manuscript with substantial input from K.P., S.S., X.A. and R.B. S.S. and R.B. were primarily responsible for the final content of the manuscript and decision to publish. All authors critically reviewed the first draft and made substantial writing contributions to the development of the final manuscript. All authors had full access to all the data in the study. D.G. and R.B. verified the underlying data of the study. The principal investigators (R.B. and S.S.) had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

A data sharing plan is available in clinicaltrial.gov. In accordance with the International Committee of Medical Journal Editors, the data generated by the trial will be made available after 6 months and ending 36 months following article publication. After this timepoint, the data will be available on request to the corresponding author to researchers who can demonstrate a methodologically sound proposal and whose proposed use of the data has been approved by an independent review committee.

Declaration of interests

K.P. serves on the Social Purposes Advisory Commission of Nutriset, a main producer of lipid-based nutrient supplement products. All other authors declare no competing interests.

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This study was developed as part of the Clinical and Operational Research Alliance (CORAL). The aim of this research platform is to develop high-quality innovative and transformative research programmes through a partnership between scientists from the research institute INSERM (Institut National de la Santé et la Recherche Médicale, Bordeaux, France, and Abidjan, Côte d'Ivoire) and the humanitarian organisation ALIMA (Paris, France, and Dakar, Senegal), primarily on improving maternal and child health outcomes. A board of directors defines the scientific policy of the CORAL partnership, along with the supervision of research projects and dissemination of results. It consists of senior representatives from both ALIMA and INSERM: Renaud Becquet (Methodological chair, INSERM, Bordeaux, France), Susan Shepherd (Cinical chair, ALIMA, Dakar, Senegal), Augustin Augier (ALIMA, Paris, France), Moumouni Kinda (ALIMA, Dakar, Senegal), Marie Jaspard (ALIMA and INSERM, Abidjan, Côte d'Ivoire), Claire Levy-Marchal (ALIMA, Paris, France), and Xavier Anglaret (INSERM, Bordeaux, France, and Abidjan, Côte d'Ivoire). The CORAL research platform meets annually with an external scientific advisory board to review projects and strategic orientation.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101878.

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