The Journal of Nutrition 155 (2025) 612–620

THE JOURNAL OF NUTRITION

journal homepage: https://jn.nutrition.org/

Community and International Nutrition

Acceptability of Microbiota-Directed Complementary Foods in Treating Indian Children with Moderate Acute Malnutrition: eACT-MAM Pre-Proof-of-Concept Study

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A B S T R A C T

Background: In India, currently, there are no standard guidelines for the management of moderate acute malnutrition (MAM). Previous research in Bangladesh has shown that children with MAM have impaired gut microbiota development, and microbiota-directed complementary foods (MDCF) can potentially repair their gut microbiota.

Objectives: The objectives of this study were to evaluate the acceptability and safety of supplementing shelf-stable formulation of MDCF in Indian children with MAM as compared with a locally prepared ready-to-use supplementary food (RUSF) in 3 geographically distinct Indian populations and to establish and pilot systems of intervention delivery, collection, transport, and storage of stool samples using stringent protocols.

Methods: This pre-proof-of-concept (prePOC), multicentric, open-labeled, age-stratified, randomized controlled trial was done in children aged 6–18 mo with MAM. After a run-in period of 2 wk, the participants were supplemented with MDCF or RUSF for 4 wk through direct observation and followed up for another 2 wk post intervention. Maternal responses to the acceptability of the organoleptic properties of supplements were recorded weekly during the intervention phase of 4 wk. Compliance was reported based on the amount of supplement consumed by the children. Feasibility of weekly stool sample collection (except 7th week) within 30 min of passage was recorded. Anthropometric measurements were done at baseline and endline. Monitoring for adverse events was done throughout the course of the study.

Results: A total of 240 children with MAM were randomly selected to receive either MDCF or RUSF, of which 221 (92.1%) completed follow-up. The overall acceptability for >80% of the maternal responses was reported as good or very good for all organoleptic properties in both MDCF and RUSF arms. MDCF and RUSF interventions had good-to-high compliance in 83.0% and 79.8% of participants, respectively. At the end of the intervention phase, 53.2% (58/109) of children in MDCF arm against 42.0% (47/112) in RUSF arm had weight-for-length *Z* score >–2. The overall incidence of acute gastroenteritis reported was low; higher in MDCF compared with RUSF but not statistically significant.

Conclusion: The prePOC study demonstrates good acceptability and safety of MDCF among Indian children with MAM including the age group of 6–12 mo of age. The study demonstrates the feasibility of conducting a long-term supplementation study in this population. The study was registered at the clinical trial registry of India as CTRI/2023/01/048716.

Keywords: food supplement, moderate acute malnutrition, acceptability, MDCF, pre-proof of concept

Abbreviations: CI, confidence interval; eACT, eliminate malnutrition through action research in MAM children; FGD, focus group discussion; IDI, in-depth interview; LAZ, length-for-age Z score; LSCS, lower segment cesarean section; MAM, moderate acute malnutrition; IQR, interquartile range; MDCF, microbiota-directed complementary food; MUAC, mid-upper arm circumference; POC, proof-of-concept; PrePOC, pre-proof-of-concept; RUSF, ready-to-use supplementary food; SAM, severe acute malnutrition; WAZ, weight-for-age *Z* score; WLZ, weight-for-length *Z* score.

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https://doi.org/10.1016/j.tjnut.2024.11.001

Received 26 July 2024; Received in revised form 23 October 2024; Accepted 1 November 2024; Available online 5 November 2024

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Introduction

Optimal nutrition is a fundamental right of every child. Acute malnutrition or wasting is a condition where a child has lower than normal weight for his or her length or is thin [mid-upper arm circumference (MUAC) <125 cm] [1]. Children with acute malnutrition or wasting, particularly in its severe form, have a higher risk of infections and death and are also associated with long-term adverse consequences on growth and development. In 2022, ~45 million under-5 children were wasted, of which more than half were from South Asia with India being the largest contributor [2]. The National Family Health Survey 5 (2019–2021) in India showed that among the under-5 children surveyed, 19.3% were wasted [weight-for-length *Z* score (WLZ) < –2 SD as per WHO 2006 growth standards]; 11.6% had moderate wasting [weight-for-age *Z* score (WAZ) between –2 and –3 SD] and 7.7% had severe wasting (WLZ < –3 SD) [3]. The greatest risk of malnutrition or wasting occurs during the first 2 y of life and is associated with insufficient complementary feeding [4]. Globally and in India, the treatment efforts are largely focused on children with severe acute malnutrition (SAM) [5,6]. Children with moderate acute malnutrition (MAM), if not treated timely and adequately, can progress into SAM. Currently, there is no clear consensus or guidelines for the treatment of children with MAM in the country.

It has been demonstrated that childhood nutrition and growth are closely linked to microbial communities in the gut [7,8]. Recent studies have demonstrated impaired gut microbiota development in children with acute malnutrition during the first 2 y of life, with lower microbiota-for-age *Z*-score compared with healthy infants [9]. It is postulated that treatment efforts should be directed to repair the defects in the gut microbiome beyond providing merely a ready-to-use supplementary food (RUSF) for better and sustained results. MDCF is a specialized food supplement developed through a series of research studies conducted in Bangladeshi children aged 12–18 mo that has demonstrated the potential for repairing the defect in gut microbial communities [10,11]. Despite the lower caloric density, children with MAM receiving MDCF showed a significantly faster rate of weight gain as compared with the control group consuming RUSF [10,11]. Given the high burden of MAM, it is important to evaluate the efficacy of MDCF in Indian children with MAM aged between 6 and 18 mo in geographically and anthropologically distinct populations. Before testing the efficacy, it is necessary to test the acceptability and safety of the MDCF formulation given the diverse eating habits in different geographic locations in India.

The objective of the present pre-proof-of-concept (prePOC) study was to evaluate the acceptability and safety of the shelf-stable formulation of MDCF compared with an RUSF in Indian children with MAM aged between 6 and 18 mo at 3 different geographic sites. We also aimed to establish and pilot test the processes of intervention delivery, specimen collection, transport, and storage at –80°C and to demonstrate the feasibility of conducting a POC study.

Methods

Study design

This was an open-label age-stratified randomized controlled trial conducted in 240 Indian children aged 6–18 mo with MAM (WLZ: < –2 to –3). The age strata included 6 to <12 and 12–18 mo.

Study population

The study was conducted in low-to-mid socioeconomic neighborhoods at 3 sites in India—Centre for Health Research and Development—Society for Applied Studies, New Delhi; Community Health Research Unit of KEM Hospital Research Centre, Pune; and Christian Medical College, Vellore. The Delhi and Vellore populations were urban whereas the Pune population was rural. Each site enrolled 80 children with noncomplicated MAM into the study (40 children aged 6 to <12 mo and 40 children aged 12–18 mo).

Approvals

The study was conducted as per ethical guidelines for biomedical Research on Human Subjects by Indian Council of Medical Research and guidelines (2017) outlined by the institutional ethics committees. The study was undertaken after approval from the institutional ethics committees of the 3 institutions. The study was registered at the clinical trial registry of India (CTRI/2023/01/048716). The trial was closely monitored by Data Safety Monitoring Board for monitoring and assuring the safety of the study participants.

Study procedures

Eligible children with MAM were identified through house-to-house prescreening. Anthropometric measurements such as weight, length, head circumference, and MUAC were collected using a Seca 354 digital weighing scale (accurate ≤10 g), a Seca 417 infantometer (accurate ≤0.1 cm), and a Seca 212 measuring tape (accurate ≤0.1 cm), respectively. WLZ was calculated using WHO Anthro Calculator. Children were enrolled after written informed consent from their parents. Children with major congenital anomalies or growth disorders, significant medical illness in the past 2 wk, antibiotic usage in the past 2 wk, and known allergy to peanuts, soy, or milk protein were excluded. Children identified with SAM or with MAM but not eligible for enrolment were referred to Anganwadi or primary health care centers for further management. The eligible participants were randomly assigned in 1:1 ratio to MDCF or RUSF arms. Information on breastfeeding, diet, vaccination, and sociodemographic characteristics was collected at baseline.

After a run-in period of 2 wk, the participants were initiated on the supplementation for a period of 4 wk. Each child was offered the supplement twice a day i.e., morning and evening. The treatment phase was followed by a follow-up phase of 2 wk. Anthropometric parameters were measured at baseline, 2, 6, and 8 wk from enrolment. Stool samples were collected every week from enrolment until the end of the postintervention period (week 8) except for week 7. Any adverse events related to or not related to the study were also captured during the stool follow-up visits.

Study intervention

The MDCF formulation (Supplemental Table 1) was prepared freshly every morning locally in the site-specific food processing laboratory using locally procured food ingredients [10,12]. We used green banana powder instead of fresh bananas as used in the earlier trial in Bangladesh [13] to prepare a shelf-stable formulation.

An isocaloric formulation of RUSF (Supplemental Table 1) was centrally prepared by a company and used across all sites. The RUSF was prepared considering ingredients that are easily available and consumed at all sites while maintaining a clear distinction in the monosaccharide content with MDCF. The micronutrient mix (vitamin and mineral) was procured centrally and added in equal quantities to both MDCF and RUSF. The protein-energy ratio and fat-energy ratio of both MDCF and RUSF were similar (Supplemental Tables 1 and 2). The daily amounts of MDCF and RUSF were calculated using daily requirements of MAM children such that the supplement would provide 25%–30% of the daily energy requirement for the study participants [14]. Children aged 6 to <12 mo were offered 18 g of MDCF/RUSF per meal (i.e., 36 g supplement daily) and children aged 12–18 mo were offered 25 g of MDCF/RUSF per meal (i.e., 50 g supplement daily).

Feeding of MDCF/RUSF to the study participants was directly supervised daily by the research team. In case of refusal for feeding by the child, efforts were made to reoffer the supplement after a 2-min pause (≤3 refusals). The duration of the feeding episode was noted and the amount of leftover food was weighed.

For quality control, a random sample from the prepared diets at each site was subjected to a panel of microbiologic investigations (total plate count, Coliform/*Escherichia coli*, Enterobacteriaceae, *Bacillus cereus*, Staphylococci, Salmonella, Shigella) at Bureau Veritas (India) Private Limited accredited by the National Accreditation Board for Testing and Calibration Laboratories [15]. The panel of tests also included pH, moisture content, total aflatoxin, yeast, and mold count.

Study outcomes

Assessment of acceptability was done at weeks 3, 4, 5, and 6 after enrolment by asking a question to the caregivers/mothers about whether the child enjoyed the supplement. The responses were categorized as "Yes, always," "Yes, but refused sometimes," "No, but can eat with some force," and "No, not at all." Perception and assessment of organoleptic characteristics (color, aroma, flavor, texture, and overall liking) of the MDCF or RUSF by the respective mother/caregiver were assessed by using the 7-point Hedonic scale. The Hedonic scale is a Likert scale where a higher value, i.e., 7, is ranked as "like extremely" and the lowest value 1 is ranked as "dislike extremely."

The compliance was categorized as "High compliance," if the child consumed ≥50% of per day supplement for ≥90% (≥25 d) of the 4-wk intervention period; "Good compliance," if child consumed ≥50% of per day supplement for 70%–89% (22–24 d) of the 4-wk period; "Partial compliance," if child consumed ≥50% per day supplement for <70% (<22 d) in the 4-wk period.

In-depth interviews (IDIs) and focus group discussions (FGDs) were conducted among caregivers/mothers of the study participants from both study arms at the end of the intervention to understand their perceptions about the study intervention, feedback on the quality, taste, and texture, and overall acceptance of the intervention. A total of 30 IDIs and 6 FGDs were conducted for this purpose.

Statistical analysis

In our prePOC study, the sample size was based on the earlier prePOC trial conducted in Bangladesh [10] which included 15 children in each arm within the age group 12–18 mo. In this trial, we planned to recruit 20 children in each trial arm (i.e., MDCF and RUSF) within each of the age strata of 6 to <12 mo and 12–18 mo, considering a loss to follow-up of 20%. A total of 80 MAM children were recruited for this prePOC study in each of the 3 sites.

All the data were captured in electronic case record forms prepared in REDCap [16] with in-built real-time quality control systems. The baseline descriptive analysis and safety analysis were conducted in all randomly selected participants. The acceptability and compliance outcomes were calculated for all participants who received the intervention at least once during the intervention period. For continuous variables, mean ± SD or median and interquartile range (IQR) were estimated. For categorical variables, count and proportions were calculated. DietCal software [17] was used to estimate total daily protein and energy intake. Overall acceptability was calculated as cumulative proportion of responses for each physical characteristic over the 4 wk through collected acceptability data. For anthropometry outcomes, mean difference and 95% confidence interval (CI) between the MDCF and RUSF arms were estimated.

For the qualitative data analysis, the data collected from IDIs and FGDs were recorded, transcribed, and then translated into English language. The data were analyzed with an inductive approach to identify codes, subthemes, and themes using DeDoose (Version 9.0.107) [18].

Results

A total of 3593 children in the age group of 6–18 mo were prescreened to identify children with MAM across the 3 sites. Among these, 326 (9.1%) were identified with MAM and were approached for study participation as shown in Figure 1. Out of these, 240 were recruited into the study. The major reasons for nonparticipation were consent refusal (10.7%) and plan for outmigration (10.7%) (Figure 1). Of the 240 children recruited, 221 (92.1%) children completed 4 wk of intervention and completed additional follow-up of 2 wk after the completion of the intervention period.

The median age with IQR of the recruited children at baseline was 11.96 (8–16) mo; around half (48.3%) were girls. The baseline characteristics were similar across the RUSF and MDCF arms except for the differences in gender and birth order (Table 1). Comparisons of baseline characteristics between the sites are given in Supplemental Tables 3 and 4.

Acceptability of the food supplement

At 4 wk after supplementation, the overall acceptability was reported as "good" by >80% of all the maternal/caregiver responses for all organoleptic properties in both MDCF and RUSF arms and was similar across the 2 age strata. For food texture, a lower proportion (76.7%) reported good acceptability in the 6 to <12 mo age category in MDCF arm. The overall liking was rated as good in 92.5% of the responses in the RUSF arm and 88.0% in the MDCF arm (Figure 2 and Supplemental Table 5). In more than two-third of the responses, mothers reported that the child enjoyed the food supplement in both arms and in >80% of the responses, mothers reported that the child completed the food supplements most of the times (Supplemental Table 6).

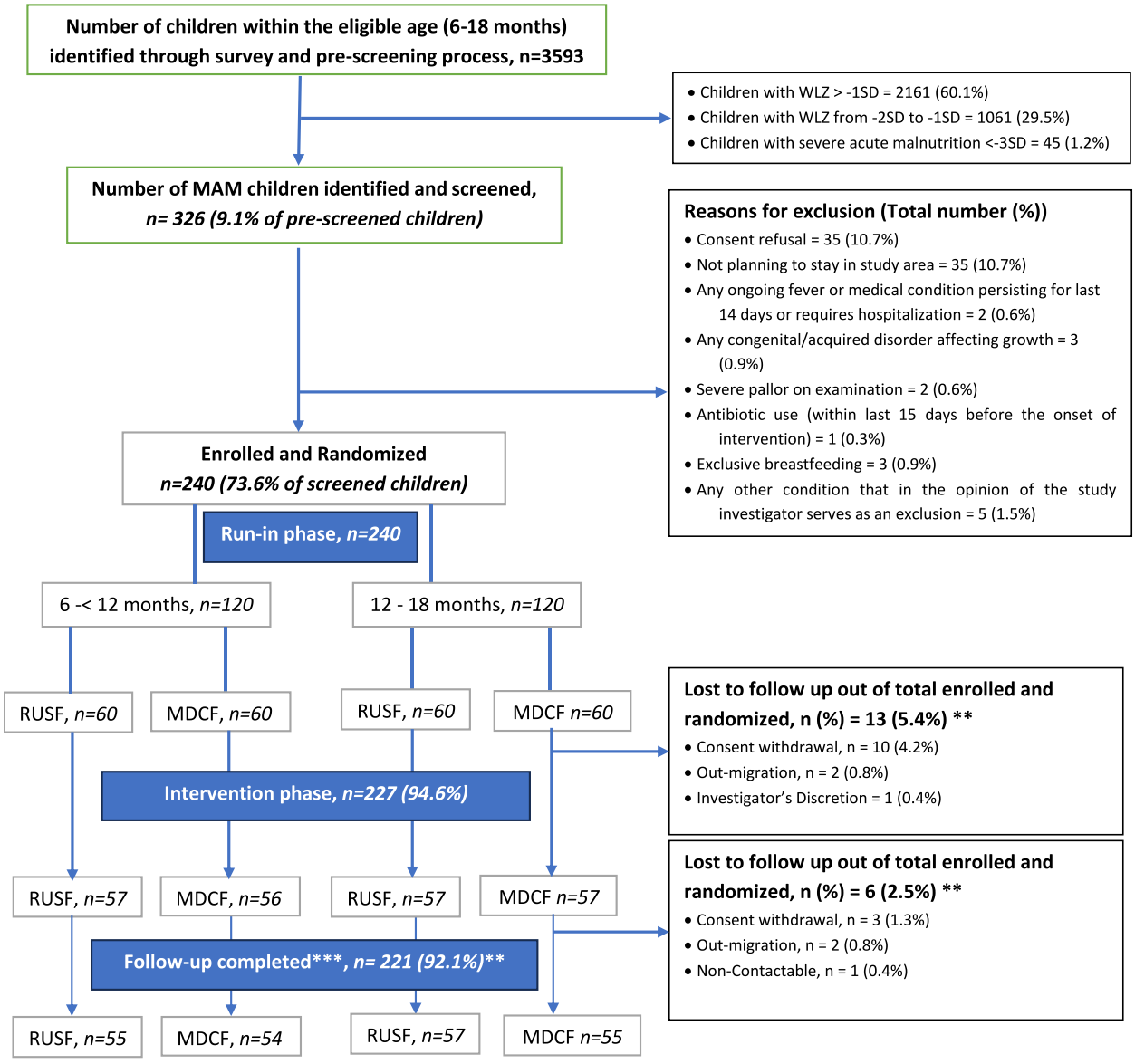

FIGURE 1. Study flowchart. *Numbers depict *n* (%). **Percentage out of total enrolled and randomly assigned. ***Children have been included in the analysis if data pertaining to a particular analysis were available for them. For example, if baseline data are available for the children who were lost to follow-up, they would have been included in the "n" in baseline tables, and similarly for other relevant tables. Hence, the "n" may differ from table to table and specified accordingly. MAM, moderate acute malnutrition; MCDF, microbiota-directed complementary food; RUSF, ready-to-use supplementary food; WLZ, weight-for-length *Z* score.

Compliance to the food supplement

Of 240 enrolled children, 227 (94.5%) children received ≥1 meal of food supplement. The mean days of food supplementation were 26.01 ± 4.46 d in the RUSF arm and 26.01 ± 4.91 d in the MDCF arm (Table 2). High compliance was observed in 71.9% (82/114) of the RUSF arm participants and 68.7% (77/112) of the MDCF arm participants. A larger proportion of children with high compliance was observed in the 6 to <12 mo age group (RUSF—73.7%; MDCF—71.4%) than in the 12–18 mo age group (RUSF—70.2%; MDCF—66.1%) for both MDCF and RUSF arms (Table 2).

Feasibility of stool sample collection

A total of 1920 samples were expected from all the recruited participants across the 8 timepoints of sample collection (Figure 2). Of these, we were able to collect 92.9% (1783/1920) of the samples. Overall high feasibility of sample collection was established by collecting 96.5% of samples within 30 min of stool passage with median collection time of 19 min. Also, 94.5% of samples were collected within a window period of 48 h from the due date of sample collection (Supplemental Table 7).

Anthropometric measurements

In both the age strata, mean of the anthropometric parameters, WLZ, weight-for-age *Z* score (WAZ), and LAZ, and the mean change in WLZ, WAZ, and LAZ from baseline to 6 or 8 wk were greater in the MDCF arm as compared with RUSF arm although the 95% CI was imprecise for all timepoints. The mean change in WLZ from baseline to end of supplement (6 wk) was 0.30 ± 0.36 in the MDCF arm as compared with 0.27 ± 0.39 in the RUSF arm.

TABLE 1
Sociodemographic and birth-related factors in MDCF and RUSF arms.

Parameters	RUSF (n = 120)	MDCF (n = 120)
Age of child at recruitment in months, mean (SD)	11.96 (4.1)	11.96 (3.8)
Number of female children, *n* (%)	51 (42.5)	65 (54.2)
Child characteristics[1]		
Birth order, *n* (%)		
1	61 (50.8)	41 (34.5)
2	38 (31.7)	63 (52.9)
3 or more	21 (17.5)	15 (12.6)
Birth weight (kg), mean (SD)	2.52 (0.54)	2.73 (0.50)
Gestational age in weeks at birth, median (IQR)	37 (36–39)	38 (36–39)
Place of delivery, *n* (%)		
Health facility	119 (99.2)	110 (92.4)
Home	1 (0.8)	9 (7.6)
Mode of delivery, *n* (%)		
Vaginal delivery	86 (71.7)	88 (74.0)
LSCS	34 (28.3)	31 (26.0)
Time of initiation of breastfeeding, *n* (%)		
Within 1 h of birth	41 (34.2)	50 (42.0)
After 1 h	79 (65.8)	68 (57.1)
Never breastfed	0	1 (0.9)
Immunization status, *n* (%)[2]		
Complete	89 (74.8)	86 (73.5)
Partial	30 (25.2)	31 (26.5)
Maternal characteristics[1]		
Maternal age (y), median (IQR)	25.5 (23–29)	26 (23–30)
Maternal education in no. of years, median (IQR)	11.5 (9–13)	10 (8–12)
Maternal occupation, *n* (%)		
Homemaker	97 (80.9)	99 (83.2)
Professional	1 (0.8)	0
Service worker	4 (3.3)	2 (1.7)
Others	18 (15.0)	18 (15.1)
Maternal BMI (kg/m^2) at time of enrolment of child, mean (SD)	22.75 (5.3)	22.48 (5.2)
Breastfeeding and diet characteristics[3]		
Any breastfeeding at the time of enrolment, *n* (%)	109 (91.6)	104 (90.4)
Total daily energy (kcal) intake based on 24-h recall at baseline, median (IQR)	714.05 (509.55–911.36)	641.2 (486.20–823.35)
Total daily protein (g) intake based on 24-h recall at baseline, median (IQR)	16.02 (9.81–24.52)	14.96 (10.33–20.28)
Socioeconomic status, *n* (%)[4]		
Poorest	19 (16.4)	28 (23.7)
Very poor	26 (22.4)	21 (17.8)
Poor	23 (19.8)	23 (19.5)
Less poor	22 (19)	25 (21.2)
Least poor	26 (22.4)	21 (17.8)

Abbreviations: LSCS, Lower Segment Cesarean Section; MCDF, microbiota-directed complementary food; RUSF, ready-to-use supplementary food.
[1] Data are available for 239 participants—120 in RUSF and 119 in MDCF group.
[2] Data are available for 238 participants and of which no data are available in the vaccination card—119 in RUSF and 117in MDCF; complete immunization status is defined as if the child received 1 dose of BCG, 3 doses of OPV, and 3 doses of pentavalent vaccine if the age is <275 d and if the age is 275 and above it includes measles containing vaccine in addition to the above.
[3] Data are available for 234 participants and one of them were never breast fed from the child birth itself—119 in RUSF and 115 in MDCF group.
[4] Data are available for 234 participants—116 in RUSF and 118 in MDCF group.

The mean change in WLZ from baseline to end of follow-up (8 wk) was 0.23 ± 0.42 in the MDCF arm as compared with 0.21 ± 0.45 in the RUSF arm. Similar pattern of change was observed in WAZ and LAZ parameters. At the end of the intervention phase (6 wk), 53.2% (58/109) of the MAM children in MDCF arm and 42.0% (47/112) of the MAM children in RUSF arm had a WLZ score >–2. (Figure 2, Supplemental Figure 1, and Supplemental Table 8).

Adverse events

Respiratory tract infections were the most reported adverse events and were similar across the MDCF and RUSF arms (Supplemental Table 9). Acute gastroenteritis was found to be slightly higher in the MDCF arm as compared with the RUSF arm probably because of initial episodes of loose stools reported in a few babies after initiation of MDCF and was not statistically significant. However, after categorizing them into events that resulted during the run-in phase, after initiation of intervention, and in the postintervention phase, the numbers were found to be similar across the arms. No allergic reactions or serious adverse events were reported.

Perception of the mothers about food supplementation

The findings from the qualitative interviews showed that the acceptability of supplementation in both arms were found to be good as most of the infants enjoyed the meals and eagerly ate finishing within 10–15 min of delivery (Figure 3).

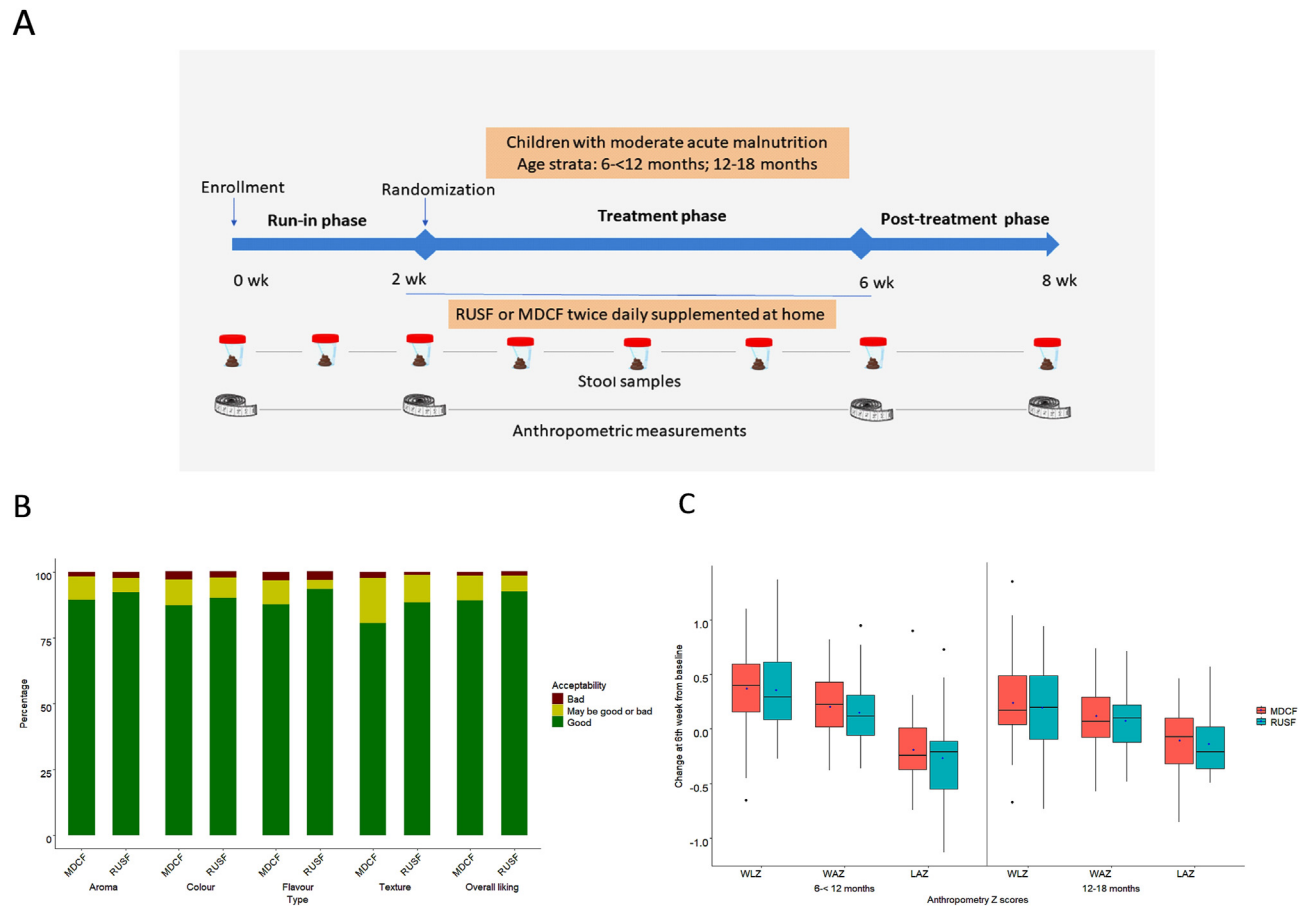

FIGURE 2. Panel showing the study flow diagram, overall acceptability for the food supplement and changes in anthropometric measurements associated with MDCF and RUSF arms. (A) Study design of eACT-MAM prePOC study. (B) Overall acceptability to organoleptic properties of food supplements in MDCF and RUSF arms. Good includes super good, really good, and good; bad includes super bad, really bad, and bad. "n" includes the total number of acceptability data collected across 4 timepoints (end of each week over 4 wk of intervention) from children recruited who had ≥1 acceptability assessment done. (C) Change in different anthropometry Z scores at 6th week from the baseline in MDCF and RUSF arms. eACT, eliminate malnutrition through action research in MAM children; MAM, moderate acute malnutrition; MCDF, microbiota-directed complementary food; PrePOC, pre-proof-of-concept; RUSF, ready-to-use supplementary food; WAZ, weight-for-age *Z* score; WLZ, weight-for-length *Z* score.

TABLE 2
Compliance toward food supplement in MDCF and RUSF arms.

Children who received ≥1 dose of intervention (n = 227)	Overall		6–<12 mo		12–18 mo	
	RUSF (n = 114)	MDCF (n = 113)	RUSF (n = 57)	MDCF (n = 56)	RUSF (n = 57)	MDCF (n = 57)
Number of days of consumption of supplement, mean (SD)	26.01 (4.46)	26.01 (4.91)	25.98 (5.39)	26.38 (4.22)	26.04 (3.35)	25.66 (5.52)
Percentage average per day consumption of food supplement, mean (SD)	87 (14)	87 (14)	88 (14)	88 (14)	86 (15)	86 (15)
No. of days in which ≥50% of per day supplement consumed per child, median (IQR)	27 (23–28)	27 (23–28)	27 (24–28)	27 (24–28)	27 (23–28)	26 (23–28)
Children who consumed ≥50% of supplement on ≥1 day (n = 226)[1]	Overall RUSF, n (%) (n = 114)	MDCF, n (%) (n = 112)	6–<12 mo RUSF, n (%) (n = 57)	MDCF, n (%) (n = 56)	12–18 mo RUSF, n (%) (n = 57)	MDCF, n (%) (n = 56)
High compliance[2]	82 (71.9)	77 (68.7)	42 (73.7)	40 (71.4)	40 (70.2)	37 (66.1)
Good compliance[3]	9 (7.9)	16 (14.3)	5 (8.8)	7 (12.5)	4 (7.0)	9 (16.1)
Partial compliance[4]	23 (20.2)	19 (17)	10 (17.5)	9 (16.1)	13 (22.8)	10 (17.8)

Abbreviations: MCDF, microbiota-directed complementary food; RUSF, ready-to-use supplementary food.
[1] One child out of 227 has not consumed ≥50% supplement on any of the days of feeding.
[2] High compliance, if the child consumed ≥50% of per day supplement ≥90% (≥25 d) of the 4-wk intervention period.
[3] Good compliance, if child consumed ≥50% of per day supplement for 70%–89% (22–24 d) of the 4-wk period.
[4] Partial compliance, if child consumed ≥50% per day supplement for <70% (<22 d) in the 4-wk period.

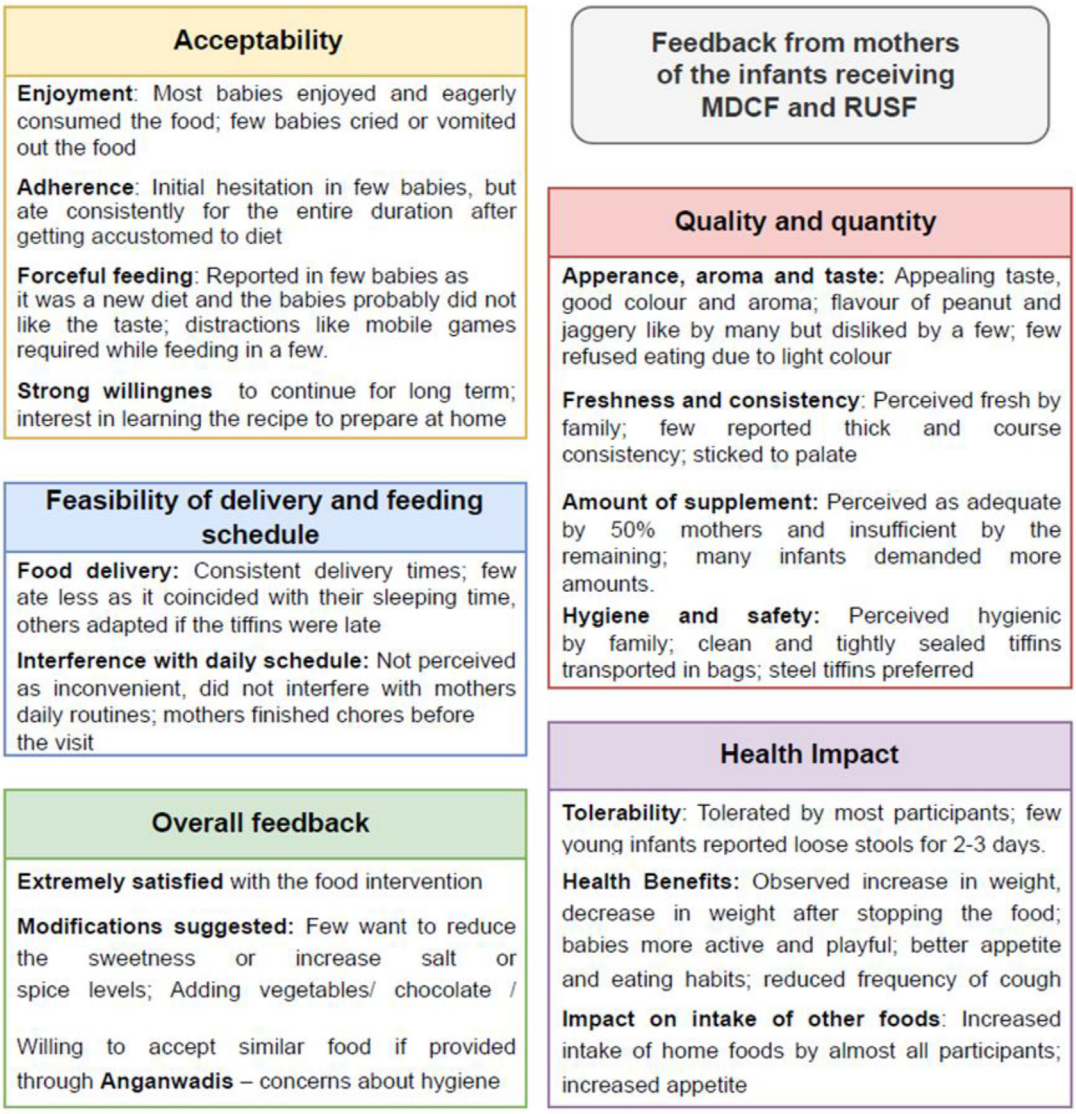

FIGURE 3. Perception of mothers about feasibility and acceptability of food supplementation. MCDF, microbiota-directed complementary food; RUSF, ready-to-use supplementary food.

In both arms, although a few infants showed hesitation or dislike initially, later most of them continued for the entire duration of the study. The caregivers, mostly mothers of the participants, were satisfied about the food appearance, aroma, color, and flavor and appreciated freshness and cleanliness of the daily food delivered. There were suggestions on the inclusion of different flavors, increase in the quantity, and addition of vegetables. In terms of food consistency, many mothers noted that the food was thick and stuck to the infant's palates, making it difficult for them to swallow. The mothers reported that they observed weight gain in the child at the end of supplementation along with increase in appetite, increased motor activity, and reduced tendency for illnesses. Mothers of few young infants reported loose stools for the initial 2–3 d after initiation of the intervention which were resolved later. No concern was expressed regarding observed feeding session. Most of the mothers showcased willingness for continuation of food supplementation for weight gain of the infants, proposing to extend the duration. (Figure 3, Supplemental Table 10).

Discussion

Our feasibility study on MDCF across Indian children with MAM from different geographic locations within India showed good acceptability of this food supplement among 6–18 mo children and their caregivers/mothers with good-to-high compliance among the majority of the participants. The acceptability among the younger age group (6 to <12 mo) was found to be good and similar to the older age group children (12–18 mo). A qualitative study conducted in parallel to this trial also demonstrated good social acceptability among the caregivers/mothers and willingness for long-term supplementation and also provided valuable feedback on the organoleptic properties of the MDCF. The observations from this study also illustrate the safety of MDCF among Indian children aged 6 to <12 mo and 12–18 mo when supplemented for a period of 4 wk and its potential use for longer durations. The high percentages of stool samples collected within 30 min demonstrate the feasibility of conducting a longer study among the larger population with stringent criteria for

stool collection. Although this study was not powered to demonstrate a statistically significant difference in the anthropometric parameters considering small sample size and short duration of intervention, MDCF seemed to be associated with higher mean WLZ, WAZ, and LAZ at all timepoints including the end of the intervention.

Earlier studies have demonstrated that gut microbiome of children with MAM and SAM have altered the representation of growth-associated bacteria taxa and microbial genes thus resulting in microbial community configuration that resembles that of chronologically younger children. Microbiota-directed foods have the potential to repair the perturbations in the configuration of microbial communities among children with SAM and MAM thus improving growth and development in these children. [11] In agreement to this, the improvement in WLZ of ~0.3 units in both the arms reported from our study is similar to that reported from the earlier prePOC study conducted in Bangladeshi children [10].

Despite the smaller sample size, the age-stratified block randomization resulted in a balance in the number of participants between the arms. This eventually resulted in an equal probability for all the participants to be in either one of the arms before their allocation into the study and we were able to minimize the selection bias. Two weeks of run-in phase before initiation of intervention aided to reduce attrition. The lower dropout rates and the quality follow-up of the participants showed the robustness of the data captured and the feasibility of the sites for a bigger efficacy trial. We also standardized the team involved in the anthropometric measurements across all the sites, to minimize measurement bias in anthropometric outcomes. Additionally, to the best of our knowledge, this is the first trial to assess the safety and acceptability of MDCF in children <12 mo of age. Low risk of bias and data from 3 different geographic locations suggest the generalizability of the results to all children of similar age from India and possibly to the Southeast Asian region.

There is a possibility of information bias given that this study was an open-labeled randomized controlled trial of food supplementation and the research teams were not blinded. To minimize this possible bias, we used different field teams for intervention delivery and outcome assessment. Another limitation of this study was that the acceptability measures that we presented in this study were merely based on the perception of the caregivers/mothers; however, the compliance calculated from the total amount of food consumed by the children, based on non-forceful feeding, is assumed to be comparable to the acceptability reported by the caregivers/mothers. Moreover, a similar acceptability in both food supplements can be because of the presence of locally available ingredients and familiar taste. Additionally, we managed to procure the control RUSF supplement centrally as a premix, but the MDCF preparations were mainly based on the locally available ingredients in each of the sites. The nutritive values can be influenced by environmental and climatical factors of the sites but interestingly the results from the food samples tested for quality control revealed a comparable result.

The acceptability and safety of the food supplement in the 3 different sites and the likely benefit in anthropometric parameters despite the short duration of intervention provide a basis for undertaking a larger POC study for MDCF among toddlers in different geographic locations in India. If proven effective, MDCF can be an effective way to treat MAM in children in India and eventually, it can evoke policy recommendations.

In conclusion, the prePOC study demonstrates good acceptability and safety of MDCF among Indian children with MAM including the age group of 6–12 mo of age. The study demonstrates the feasibility of conducting a long-term supplementation study in this population with stringent criteria for stool sample collection.

Acknowledgments

We thank Gagandeep Kang, FRS, for her guidance in conducting the study and her support in acquiring funding. We also thank Nita Bhandari, Director of SAS, and Ranadip Chowdhury, Assistant Director of SAS, for their technical inputs for the conduct of the study. Additionally, we would like to thank Dilip Abraham for his contributions to the laboratory technical aspects. We acknowledge Jeffrey I. Gordon and Michael J. Barratt from Washington University School of Medicine, St. Louis, United States, for their valuable inputs on scientific concepts. We also thank Ishita Mostafa and Tahmeed Ahmed from the International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh, for their insights on MDCF preparation. Additionally, we extend our gratitude to all the children, their caregivers, and the entire study team involved in the conduct of the study.

Author contributions

The authors' responsibilities were as follows – SM: had full access to all of the data in the study; SM, AA, BS: take responsibility for the integrity of the data and accuracy of the data analysis; VRM, ST, SM, AA, BS, MS: concept and design; MS, AV, SM, AA, BS, DA, GD: statistical analysis and interpretation; SM, AA, BS, MS: drafting of the manuscript; DA, GD, MS, AV, ZM, SP, GA, RC, HB: administrative, technical, or material support; VRM: supervision; and all authors: read and approved the final version of the manuscript, critical review of the manuscript for important intellectual content.

Data availability

Data will be shared upon reasonable request to the corresponding author at sammarconi@cmcvellore.ac.in after publication.

Conflict of interest

The authors report no conflicts of interest.

Funding

This study was funded by the Sun Pharma, Mumbai through corporate social responsibility scheme. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2024.11.001.

References

[1] WHO, Supplementary foods for the management of moderate acute malnutrition in children aged 6–59 months [Internet]. [cited 1 May 2024]. Available from: https://www.who.int/tools/elena/interventions/food-children-mam.

[2] WHO, Levels and trends in child malnutrition: UNICEF/WHO/World Bank Group joint child malnutrition estimates: key findings of the 2023 edition [Internet]. [cited 1 May 2024]. Available from: https://www.who.int/publications-detail-redirect/9789240073791.

[3] NFHS-5_Phase-II_0.pdf [Internet]. [cited 1 May 2024]. Available from: https://main.mohfw.gov.in/sites/default/files/NFHS-5_Phase-II_0.pdf.

[4] O. Karlsson, R. Kim, S. Guerrero, A. Hasman, S.V. Subramanian, Child wasting before and after age two years: a cross-sectional study of 94 countries, eClinicalMedicine 46 (2022) 101353.

[5] WHO, Guideline: updates on the management of severe acute malnutrition in infants and children [Internet]. [cited 1 May 2024]. Available from: https://www.who.int/publications-detail-redirect/9789241506328.

[6] CMAM-Book-10-10-2023 (1).pdf [Internet]. [cited 1 May 2024]. Available from: https://wcd.nic.in/sites/default/files/CMAM-Book-10-10-2023%20%281%29.pdf.

[7] S. Subramanian, L.V. Blanton, S.A. Frese, M. Charbonneau, D.A. Mills, J.I. Gordon, Cultivating healthy growth and nutrition through the gut microbiota, Cell 161 (1) (2015) 36–48.

[8] L.V. Blanton, M.R. Charbonneau, T. Salih, M.J. Barratt, S. Venkatesh, O. Ilkaveya, et al., Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children, Science 351 (6275) (2016) aad3311.

[9] A.S. Raman, J.L. Gehrig, S. Venkatesh, H.W. Chang, M.C. Hibberd, S. Subramanian, et al., A sparse covarying unit that describes healthy and impaired human gut microbiota development, Science 365 (6449) (2019) eaau4735.

[10] J.L. Gehrig, S. Venkatesh, H.W. Chang, M.C. Hibberd, V.L. Kung, J. Cheng, et al., Effects of microbiota-directed foods in gnotobiotic animals and undernourished children, Science 365 (6449) (2019) eaau4732.

[11] R.Y. Chen, I. Mostafa, M.C. Hibberd, S. Das, M. Mahfuz, N.N. Naila, et al., A microbiota-directed food intervention for undernourished children, N. Engl. J. Med. 384 (16) (2021) 1517–1528.

[12] I. Mostafa, N.N. Nahar, M.M. Islam, S. Huq, M. Mustafa, M. Barratt, et al., Proof-of-concept study of the efficacy of a microbiota-directed complementary food formulation (MDCF) for treating moderate acute malnutrition, BMC Public Health 20 (1) (2020) 242.

[13] I. Mostafa, S.M. Fahim, S. Das, M.A. Gazi, M.M. Hasan, K.N. Saqeeb, et al., Developing shelf-stable Microbiota Directed Complementary Food (MDCF) prototypes for malnourished children: study protocol for a randomized, single-blinded, clinical study, BMC Pediatr 22 (1) (2022) 385.

[14] WHO, Technical note—supplementary foods for the management of moderate acute malnutrition in infants and children 6–59 months of age [Internet]. [cited May 1, 2024]. Available from: https://www.who.int/publications-detail-redirect/9789241504423.

[15] Bureau Veritas India, Testing, inspection and certification [Internet]. [cited 2 July 2024]. Available from: https://www.bureauveritas.co.in/.

[16] Citations—REDCap [Internet]. [cited 2 July 2024]. Available from: https://projectredcap.org/resources/citations/.

[17] DietCal [Internet]. [cited 2 July 2024]. Available from: http://dietcal.in/index.html.

[18] Home, Dedoose [Internet]. [cited 2 July 2024]. Available from: https://www.dedoose.com/.