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Preterm Formula versus Human Milk Fortifier for Fortification of Mother's Own Milk in Very Low Birth Weight Infants: The PREMFORT Trial

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Abstract

Objective

To determine whether fortifying mother's own milk with preterm formula powder is non-inferior to human milk fortifier for weight growth velocity in very low birth weight (VLBW) infants.

Study Design

Single-centre, open-label, stratified, randomized non-inferiority trial. Infants < 34 weeks and < 1 500 g on ≥ 100 mL/kg/day of mother's own milk were randomized to human milk fortifier (HMF; n = 83) or preterm formula (PTF; n = 81) at 1 g/25 mL; PTF infants also received calcium, phosphorus, vitamin D, and multivitamin. Non-inferiority margin: 2 g/kg/day (90% CI).

Result

One PTF infant died before the endpoint (evaluable n = 163). Growth velocity was 13.96 (1.82) (HMF) versus 13.29 (1.88) g/kg/day (PTF); difference − 0.68 (90% CI − 1.16 to − 0.20). Sensitivity and adjusted analyses were supportive; secondary growth outcomes were similar between groups, and estimated acquisition cost was 88% lower with PTF.

Conclusion

Preterm formula with supplementation was non-inferior to human milk fortifier for short-term weight growth at substantially lower estimated cost.

Trial registration

Clinical Trials Registry–India, CTRI/2025/07/089932.

Introduction

Human milk is the preferred enteral nutrition for preterm infants but does not consistently meet the protein, energy, mineral, and micronutrient requirements of very low birth weight (VLBW) infants. Multinutrient fortification of human milk is therefore recommended and improves in-hospital weight, length, and head-circumference growth.[1,2]

Commercial bovine human milk fortifier (HMF) is the standard approach in many neonatal units but is expensive and inconsistently available in low- and middle-income settings, where these limitations restrict routine fortification.[3] Affordable, widely available alternatives that maintain growth without increasing morbidity are therefore needed.

Preterm formula powder (PTF) is one such alternative. Added in small quantities to mother's own milk, it increases nutrient delivery while preserving a predominantly human-milk diet; however, at usual doses it

does not supply sufficient calcium, phosphorus, and vitamin D and therefore requires targeted supplementation.

Several small randomized and observational studies have evaluated preterm, post-discharge, or concentrated formula preparations as alternatives to commercial HMF, with generally comparable short-term growth but heterogeneous findings for feeding tolerance and morbidity.[4,5,6,7,8,9] A recent meta-analysis of six randomized trials (434 infants) found no difference in weight, length, or head-circumference growth between formula-based and HMF fortification, but rated the certainty of evidence very low because of methodological limitations and heterogeneity.[10] The closest antecedent, a randomized non-inferiority trial by Chinnappan and colleagues, found preterm formula powder non-inferior to HMF for weight gain and associated with less feed intolerance.[6] Larger, rigorously designed non-inferiority trials remain warranted; moreover, commercial fortifiers are not standardized products and differ between manufacturers, so evidence from one formulation should not necessarily be generalized to another.

We therefore conducted the PREMFORT trial to determine whether fortification of mother's own milk with preterm formula powder, with appropriate mineral and vitamin supplementation, is non-inferior to a different commercially available bovine HMF for postnatal weight growth velocity in VLBW infants, and to compare linear and head-circumference growth, feeding tolerance, major neonatal morbidities, and the direct intervention cost of the two strategies.

Methods

Trial design and oversight

PREMFORT was a prospective, single-centre, open-label, parallel-group, stratified, randomized non-inferiority trial conducted in a level III neonatal intensive care unit at Government Medical College, Chhatrapati Sambhajinagar, India, between July 2025 and July 2026. The study was approved by the Institutional Ethics Committee, Government Medical College, Aurangabad (IEC-GMCA; approval no. Pharma/IEC-GMCA/202/2024; March 20, 2024), and was conducted in accordance with the Declaration of Helsinki. The trial was prospectively registered with the Clinical Trials Registry–India (CTRI/2025/07/089932) before enrolment of the first participant. Written informed consent was obtained from a parent or legal guardian before enrolment. Reporting followed the CONSORT 2025 Statement, applicable recommendations of the CONSORT extension for randomized trials involving children, and guidance for reporting non-inferiority trials.[11–13].

Participants

Eligible infants had a gestational age < 34 completed weeks, birth weight < 1 500 g (VLBW), were receiving ≥ 100 mL/kg/day of enteral feeds with more than 80% of intake as expressed mother's own

milk (donor human milk < 20%), and had written parental consent. Infants were excluded for major congenital malformation, requirement for surgery, absence of mother's own milk, invasive mechanical ventilation at enrolment, or any condition precluding enteral fortification.

Randomization, allocation concealment, and masking

A computer-generated sequence prepared by an independent investigator used stratified block randomization (variable blocks of 4, 6, and 8) within two a-priori gestational-age strata (< 30 and 30 to < 34 weeks), allocating infants 1:1. Eligible infants were enrolled by the principal investigator, and allocation was concealed using sequentially numbered, opaque, sealed envelopes opened only at enrolment. Because the interventions differed visibly after preparation, blinding of caregivers and clinicians was not feasible; all anthropometric outcomes were assessed by personnel unaware of allocation.

Interventions

Human milk fortifier group. Infants received expressed mother's own milk fortified with Lactodex Human Milk Fortifier (Raptakos, Brett & Co. Ltd., Thane, India) at a dose of 1 g per 25 mL of expressed breast milk. Fortification was initiated after infants tolerated enteral feeds of at least 100 mL/kg/day and continued until hospital discharge or 40 weeks' postmenstrual age (PMA), whichever occurred first.

Preterm formula group. Infants received expressed mother's own milk fortified with Dexolac Special Care Preterm Formula (Danone India Pvt. Ltd., Mumbai, India) at a dose of 1 g per 25 mL of expressed breast milk. Preterm formula powder was measured using a separate standardized 1-g measuring spoon. Because preterm formula alone did not meet targets for calcium, phosphorus, and vitamin D at this dose, these infants additionally received oral calcium and phosphorus (Calcimax-P; 3 mL/kg/day), vitamin D (800 IU/day), and a multivitamin (1 mL/day).

Oral elemental iron (2–3 mg/kg/day) was administered to infants in both groups and was therefore excluded from the comparative intervention acquisition-cost analysis. The complete fortification strategy for each group is summarized in Supplementary Figure S1.

Outcomes and definitions

The primary outcome was weight growth velocity (g/kg/day) from initiation of fortification to discharge or 40 weeks' PMA, calculated using the exponential method, $GV = [1000 \times \ln(W2/W1)] / (D2 - D1)$, where W1 and W2 are the weights at enrolment and at the endpoint and D1 and D2 the corresponding postnatal days. The exponential method accounts for changing body weight over the interval and provides a more accurate estimate of growth velocity than two-point methods in low birth weight infants.[14]

Secondary outcomes were length and head-circumference velocity (cm/week), discharge anthropometry, duration of fortification, length of hospital stay, and prespecified morbidities, each defined using an established classification: small- versus appropriate-for-gestational-age by the Fenton 2013 charts;[15] feed intolerance by the IAP Standard Treatment Guidelines (gastric residual volume > 50% of the feed, abdominal distension, and/or bilious or blood-stained aspirates prompting interruption of feeds);[16] necrotizing enterocolitis (NEC) as modified Bell stage ≥ II;[17] late-onset sepsis, operationally defined for this trial as sepsis occurring ≥ 72 hours after birth and including culture-proven sepsis and culture-negative clinical sepsis diagnosed by the treating neonatologist on the basis of compatible clinical features and supportive laboratory evidence and treated with a therapeutic course of antibiotics, in keeping with the range of definitions used in neonatal randomized trials;[18] anaemia requiring red-cell transfusion, using the transfusion thresholds of Deschmann et al.;[19] haemodynamically significant patent ductus arteriosus (PDA) requiring pharmacological or surgical treatment, based on clinical and echocardiographic assessment;[20] bronchopulmonary dysplasia (BPD) by the Jensen definition at 36 weeks' PMA;[21] retinopathy of prematurity (ROP) requiring treatment (Type 1) per ETROP;[22] severe intraventricular haemorrhage, defined as grade III intraventricular haemorrhage or periventricular haemorrhagic infarction (PVHI), according to the Volpe classification;[23] and in-hospital mortality.

Anthropometric measurements

Weight was measured using an EasyCare Baby Cum Child Scale (model EC-3402; EasyCare Global/Ranish Impex Pvt. Ltd., Mumbai, India; maximum capacity 25 kg; resolution 5 g), zeroed before each measurement. Recumbent length was measured to the nearest 0.1 cm using an infantometer, with the head positioned against the fixed headboard and the legs fully extended. Head circumference was measured to the nearest 0.1 cm using a non-stretchable measuring tape around the maximal occipitofrontal circumference. Measurements were obtained at enrolment and at the study endpoint by personnel unaware of treatment allocation.

Intervention acquisition-cost analysis

A patient-level intervention acquisition-cost analysis was performed from the hospital perspective, restricted to direct product costs (fortifier, preterm formula, and supplements); this is a cost analysis, not a cost-effectiveness or full economic evaluation. Costs were estimated, not directly measured: milk volume was assumed to be 150 mL/kg/day throughout the fortification period, using the mean of enrolment and endpoint weights as the representative weight (the endpoint weight was the discharge or 40-week weight, or the last weight before death for the infant who died). Iron was administered in both groups and excluded. Unit prices were from institutional procurement (2026). All 164 randomized infants were included in this analysis, which concerns actual intervention exposure and is separate from the primary growth analysis; the infant who died had 17 days of exposure. An institutional budget-impact

projection was additionally derived from the approximately 450 VLBW infants admitted annually, presented explicitly as a scenario analysis.

Sample size

Assuming a standard deviation of 4 g/kg/day, a non-inferiority margin of 2 g/kg/day, one-sided α = 0.05, and 90% power, 69 infants per group were required; allowing for 15% attrition, the target was 82 per group (164 total). The 2 g/kg/day margin was prespecified as the largest reduction in weight growth velocity considered clinically acceptable, consistent with the previous non-inferiority trial.[6]

Statistical analysis

The intention-to-treat population comprised all 164 randomized infants, analysed according to randomized allocation. One infant in the PTF group died before the prespecified growth endpoint; because death rendered endpoint growth velocity undefined rather than simply missing, the primary growth analysis included the 163 infants with an ascertainable endpoint (HMF 83, PTF 80). There were no protocol deviations; consequently, the per-protocol population among infants with an ascertainable primary endpoint was identical to the primary evaluable population. All 164 randomized infants were retained for clinical outcomes, including mortality. A sensitivity analysis incorporated the deceased infant's observed growth up to death.

Normally distributed data are summarized as mean (SD). The difference in weight growth velocity (PTF − HMF) was estimated by Welch's t-test with a two-sided 90% confidence interval (one-sided α = 0.05); non-inferiority was concluded if the lower limit exceeded − 2 g/kg/day. The sensitivity analysis used observed growth velocity from enrolment to the last weight before death (n = 164), a different estimand interpreted as supportive only. An adjusted linear model included gestational-age stratum and respiratory support before enrolment, and consistency across strata was examined with a treatment-by-stratum interaction term.

Non-normal continuous secondary outcomes are summarized as median (IQR) and compared with the Mann–Whitney U test (Hodges–Lehmann differences with 95% confidence intervals). Categorical outcomes are summarized as n/N (%) with odds ratios (PTF vs HMF) and 95% confidence intervals and compared with Fisher's exact test; for outcomes requiring survival to a later assessment, the infant who died before that assessment was excluded (evaluable denominators). Secondary analyses were exploratory, without adjustment for multiple comparisons. Analyses used R version 4.6.1.

Use of large language models

A large language model (Claude, Anthropic) was used during manuscript preparation for language editing and grammar only. All study design, data, statistical analyses, tables, references, and scientific content were produced and verified by the authors, who take full responsibility for the manuscript.

Results

Trial population

Between July 2025 and July 2026, 213 infants were assessed for eligibility; 49 were excluded (45 did not meet criteria — birth weight ≥ 1 500 g in 39, mechanical ventilation in 3, surgery in 2, major anomaly in 1 — and 4 declined consent). The remaining 164 infants were randomized (HMF 83, PTF 81) and all received the allocated intervention (Fig. 1). There were no losses to follow-up. One PTF infant died before the primary growth endpoint; the primary growth analysis therefore included 163 infants (HMF 83, PTF 80), and all 164 were retained for clinical outcomes.

Baseline characteristics

Baseline maternal and neonatal characteristics were generally balanced (Table 1). Median gestational age was 31.3 weeks (HMF) and 31.0 weeks (PTF), and median birth weight 1 290 g and 1 280 g, respectively. Respiratory support before enrolment was more frequent in the PTF group (82.7% vs 63.9%; standardized mean difference 0.43), the only clinically relevant imbalance.

Table 1
Baseline maternal and neonatal characteristics

Characteristic	HMF (n = 83)	PTF (n = 81)	SMD
Maternal age, y	23.0 (21.0–27.5)	24.0 (21.0–29.0)	0.07
Primigravida, n (%)	32 (38.6)	34 (42.0)	0.07
Any antenatal corticosteroid, n (%)	66 (79.5)	59 (72.8)	0.16
Hypertensive disorder of pregnancy, n (%)	25 (30.1)	32 (39.5)	0.20
Caesarean delivery, n (%)	42 (50.6)	30 (37.0)	0.27
Gestational age, wk	31.3 (29.5–33.0)	31.0 (29.6–32.5)	0.05
Birth weight, g	1 290 (1 148–1 375)	1 280 (1 100–1 350)	0.02
Male sex, n (%)	39 (47.0)	49 (60.5)	0.27
Multiple gestation, n (%)	12 (14.5)	12 (14.8)	0.01
Weight at enrolment, g	1 180 (1 030–1 290)	1 190 (1 000–1 280)	0.08
Any respiratory support pre-enrolment, n (%)	53 (63.9)	67 (82.7)	0.43
Sepsis before enrolment, n (%)	50 (60.2)	56 (69.1)	0.19

Note. Continuous variables are median (interquartile range); categorical variables n (%). Baseline characteristics are shown for all 164 randomized infants. SMD, standardized mean difference; HMF, human milk fortifier; PTF, preterm formula.

Primary outcome

Mean growth velocity was 13.96 (SD 1.82) g/kg/day in the HMF group (n = 83) and 13.29 (SD 1.88) g/kg/day in the PTF group (n = 80). The difference (PTF − HMF) was − 0.68 g/kg/day (90% CI − 1.16 to − 0.20); the lower limit exceeded the − 2 g/kg/day margin, demonstrating non-inferiority (Table 2; Fig. 2). A supportive sensitivity analysis incorporating the deceased infant's observed growth to the last weight before death (n = 164) yielded − 0.71 g/kg/day (90% CI − 1.19 to − 0.23), and an adjusted analysis − 0.67 g/kg/day (90% CI − 1.09 to − 0.25); both preserved non-inferiority.

Table 2
Primary and secondary growth outcomes

Outcome	HMF	PTF	Effect estimate (PTF − HMF)	Confidence interval (P value)
Weight growth velocity, g/kg/day	13.96 (1.82)	13.29 (1.88)	−0.68	90% CI −1.16 to − 0.20
Sensitivity analysis (n = 164)[1]	—	—	−0.71	90% CI −1.19 to − 0.23
Adjusted analysis[2]	—	—	−0.67	90% CI −1.09 to − 0.25
Length velocity, cm/week	0.88 (0.65–1.00)	0.80 (0.64–1.06)	0.00	−0.10 to 0.09 (P = 0.85)
Head-circumference velocity, cm/week	0.50 (0.44–0.62)	0.49 (0.39–0.62)	−0.01	−0.05 to 0.04 (P = 0.65)
Weight at discharge, g	1 495 (1 458–1 553)	1 493 (1 439–1 536)	−10	−30 to 15 (P = 0.45)
Length at discharge, cm	39.5 (39.0–40.5)	39.5 (38.5–40.5)	0.00	−0.50 to 0.00 (P = 0.39)
Head circumference at discharge, cm	29.0 (28.5–29.5)	29.0 (28.0–29.6)	0.00	−0.50 to 0.50 (P = 0.79)

Note. Primary non-inferiority analyses are presented with 90% confidence intervals; secondary outcomes are presented with 95% confidence intervals. Weight growth velocity is mean (SD); the difference (PTF − HMF) was estimated by Welch's t-test, and non-inferiority was concluded when the lower 90% limit exceeded − 2 g/kg/day. Secondary outcomes are median (interquartile range); differences are Hodges–Lehmann location shifts, and P values are from the Mann–Whitney U test. [1]Supportive sensitivity analysis incorporating the deceased infant's observed growth to the last weight before death (a different estimand, interpreted as supportive only). [2]Adjusted for gestational-age stratum and respiratory support before enrolment. HMF, human milk fortifier; PTF, preterm formula.

There were no protocol deviations; therefore, the per-protocol analysis was identical to the primary evaluable analysis and yielded the same estimate.

Growth velocity was lower in the PTF group within both strata. In the < 30-week stratum, the 90% confidence interval crossed the prespecified non-inferiority margin (mean difference − 1.07 g/kg/day; 90% CI − 2.02 to − 0.12); therefore, non-inferiority was not demonstrated within this subgroup. In the 30 to < 34-week stratum the mean difference was − 0.59 g/kg/day (90% CI − 1.02 to − 0.16). Subgroup analyses were descriptive and were not powered for independent non-inferiority testing, and there was no evidence of treatment-effect heterogeneity by gestational-age stratum (interaction P = 0.37; Fig. 2).

Secondary and clinical outcomes

Length velocity, head-circumference velocity, discharge anthropometry, duration of fortification, and length of hospital stay were similar between groups (Table 2). Length velocity was 0.88 cm/week (IQR 0.65–1.00) with HMF and 0.80 cm/week (0.64–1.06) with PTF, and head-circumference velocity 0.50 cm/week (0.44–0.62) and 0.49 cm/week (0.39–0.62), respectively; neither differed significantly (P = 0.85 and P = 0.65). Discharge weight, length, and head circumference were also comparable (all P > 0.39). The incidence of feed intolerance, NEC, late-onset sepsis, anaemia requiring transfusion, haemodynamically significant PDA, ROP requiring treatment, and BPD did not differ significantly between groups (Table 3). No infant developed severe intraventricular haemorrhage. One PTF infant died; no HMF infant died (Fisher exact P = 0.494).

Table 3
Clinical outcomes and neonatal morbidities

Outcome	HMF n/N (%)	PTF n/N (%)	OR (95% CI)*	P
Feed intolerance	12/83 (14.5)	11/81 (13.6)	0.93 (0.38–2.25)	1.000
NEC ≥ stage II	5/83 (6.0)	2/81 (2.5)	0.39 (0.07–2.10)	0.443
Late-onset sepsis	14/83 (16.9)	18/81 (22.2)	1.41 (0.65–3.06)	0.434
Anaemia requiring transfusion	13/83 (15.7)	13/81 (16.0)	1.03 (0.45–2.38)	1.000
Haemodynamically significant PDA	6/83 (7.2)	4/81 (4.9)	0.67 (0.18–2.46)	0.746
ROP requiring treatment	4/83 (4.8)	2/80 (2.5)	0.51 (0.09–2.85)	0.682
Bronchopulmonary dysplasia	7/83 (8.4)	4/80 (5.0)	0.57 (0.16–2.03)	0.535
Severe IVH (grade III / PVHI)	0/83 (0.0)	0/81 (0.0)	Not estimable	—
Death	0/83 (0.0)	1/81 (1.2)	Not estimable	0.494

Note. Values are n/N (%). *Odds ratio (PTF vs HMF) with 95% CI; P values by Fisher's exact test. Denominators represent infants evaluable for each outcome; the infant who died before the relevant assessment time point was excluded from outcomes requiring survival to that assessment (bronchopulmonary dysplasia at 36 weeks' PMA and retinopathy of prematurity). The odds ratio was not estimable when one group had no events. PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; IVH, intraventricular haemorrhage; PVHI, periventricular haemorrhagic infarction.

Intervention acquisition cost

The median intervention acquisition cost per infant was INR 4 255 (IQR 2 393–6 172) in the HMF group and INR 486 (IQR 304–765) in the PTF group (P < 0.001). Mean costs were INR 4 838 and INR 580 per infant, respectively, corresponding to an estimated mean saving of INR 4 258 per infant and an 88.0% reduction in intervention acquisition cost with the PTF-based strategy (Hodges–Lehmann shift INR 3 832; 95% CI 3 159–4 701). The PTF cost estimate included calcium/phosphorus, vitamin D, and multivitamin supplementation. Iron cost was excluded because iron supplementation was administered

in both treatment groups. An institutional budget-impact projection based on annual admissions is provided as a scenario analysis in the Supplementary Appendix.

Discussion

In this stratified, randomized non-inferiority trial, fortification of mother's own milk with preterm formula powder, together with mineral and vitamin supplementation, was non-inferior to commercial bovine human milk fortifier for postnatal weight growth velocity; the lower 90% confidence limit remained above the − 2 g/kg/day margin in the primary, sensitivity, and adjusted analyses. Linear and head-circumference growth, discharge anthropometry, and duration of hospitalization were similar; no statistically significant differences in major morbidities were observed; and the preterm-formula strategy was substantially less expensive.

These findings should be viewed within an evolving but heterogeneous evidence base. An early randomized pilot by Khorana and colleagues found similar growth and biochemical markers with post-discharge formula versus HMF at far lower cost.[4] Willeitner and colleagues randomized VLBW infants to concentrated preterm formula or powdered HMF and found similar weight gain and tolerance.[5] Chinnappan and colleagues, in the closest non-inferiority trial, reported non-inferior weight gain and less feed intolerance with preterm formula powder.[6] In contrast, a retrospective cohort by Al Mandhari and colleagues found higher early weight gain and less NEC with HMF than with preterm formula,[7] and a three-arm trial by Pedaveeti and colleagues found higher absolute weight and head circumference at 6 weeks with HMF but more feed intolerance than with preterm formula.[8] A quality-improvement cohort during an HMF shortage reported adequate growth with a high-calorie preterm formula.[9] A meta-analysis of six trials found no pooled difference in growth but very low certainty.[10] PREMFORT adds a comparatively large, prospectively registered non-inferiority trial to this literature.

Our trial differs in important respects from the closely related trial of Pedaveeti and colleagues, which enrolled only appropriate-for-gestational-age infants of 28–32 weeks and 1 000–1 500 g, used a three-arm superiority design, compared Lactodex against a PreNAN formula rather than Dexolac, and assessed serial absolute anthropometry rather than a prespecified exponential growth velocity.[8] Because that trial and others have already evaluated Lactodex, the contribution of PREMFORT lies in its design and scale — a prospectively registered non-inferiority framework with a defined supplementation strategy and blinded growth-velocity assessment — rather than in the novelty of any single product.

Commercial fortifiers are not standardized products; the two evaluated in the relevant trials differ chiefly in vitamin D and selected micronutrients (Supplementary Appendix). PREMFORT therefore evaluated a complete fortification strategy — preterm formula plus targeted mineral and vitamin supplementation — rather than a fortifier product in isolation, a distinction that should be preserved if the strategy is implemented.

Findings on feeding tolerance have been inconsistent across studies: some report less feed intolerance with preterm formula, others more NEC, and we observed comparable rates. This heterogeneity, together with the very low certainty of pooled evidence, indicates that equivalence of feeding tolerance and safety across formula-based strategies cannot yet be assumed.

The economic findings are relevant to resource-limited settings. Because the primary growth outcome met the prespecified non-inferiority criterion, we additionally compared intervention acquisition costs; however, this reflects direct product costs only and was estimated rather than measured, and the budget-impact projection is a scenario rather than an observed finding.

Strengths include prospective registration, gestational-age-stratified randomization with concealed allocation, blinded anthropometry, the validated exponential growth-velocity method, complete follow-up for clinical outcomes, and a prespecified sensitivity analysis for the single death. Limitations include the single-centre, open-label design; power directed at growth rather than infrequent morbidities, so comparable morbidity rates should not be interpreted as equivalence; one death as a competing event for the growth endpoint, which required an evaluable-population primary analysis; estimation rather than measurement of costs; and follow-up limited to the birth hospitalization, leaving longer-term growth, bone health, and neurodevelopment undetermined.

In conclusion, preterm formula powder with appropriate mineral and vitamin supplementation was non-inferior to commercial bovine human milk fortifier for short-term weight growth velocity in VLBW infants and was markedly less expensive. These results add a comparatively large randomized non-inferiority trial to a heterogeneous, low-certainty evidence base and suggest that preterm formula powder with appropriate supplementation may provide a practical alternative fortification strategy where commercial human milk fortifier is unavailable or unaffordable. Multicentre trials powered for clinical outcomes and long-term follow-up are needed.

Declarations

Additional Information

Ethics approval and consent. See Methods; approved by the Institutional Ethics Committee, Government Medical College, Aurangabad (approval no. Pharma/IEC-GMCA/202/2024).

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Competing interests. The authors declare no competing interests.

Data availability. De-identified data and statistical code are available from the corresponding author on reasonable request, subject to institutional approval.

Author contributions. AH — conceptualization, design, recruitment, data collection, analysis, drafting. AKJ — supervision, methodology, critical revision. ACL — supervision, patient management, critical revision. LSD (Professor and Head of Department) — study supervision, critical revision. RG — data collection, drafting; VM — data collection, drafting; GC — data collection, drafting. All authors approved the final manuscript.

Trial registration: Clinical Trials Registry–India CTRI/2025/07/089932; registered prospectively before enrolment (1 July 2025)

Ethics approval: Institutional Ethics Committee, Government Medical College, Aurangabad (approval no. Pharma/IEC-GMCA/202/2024).

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Figures

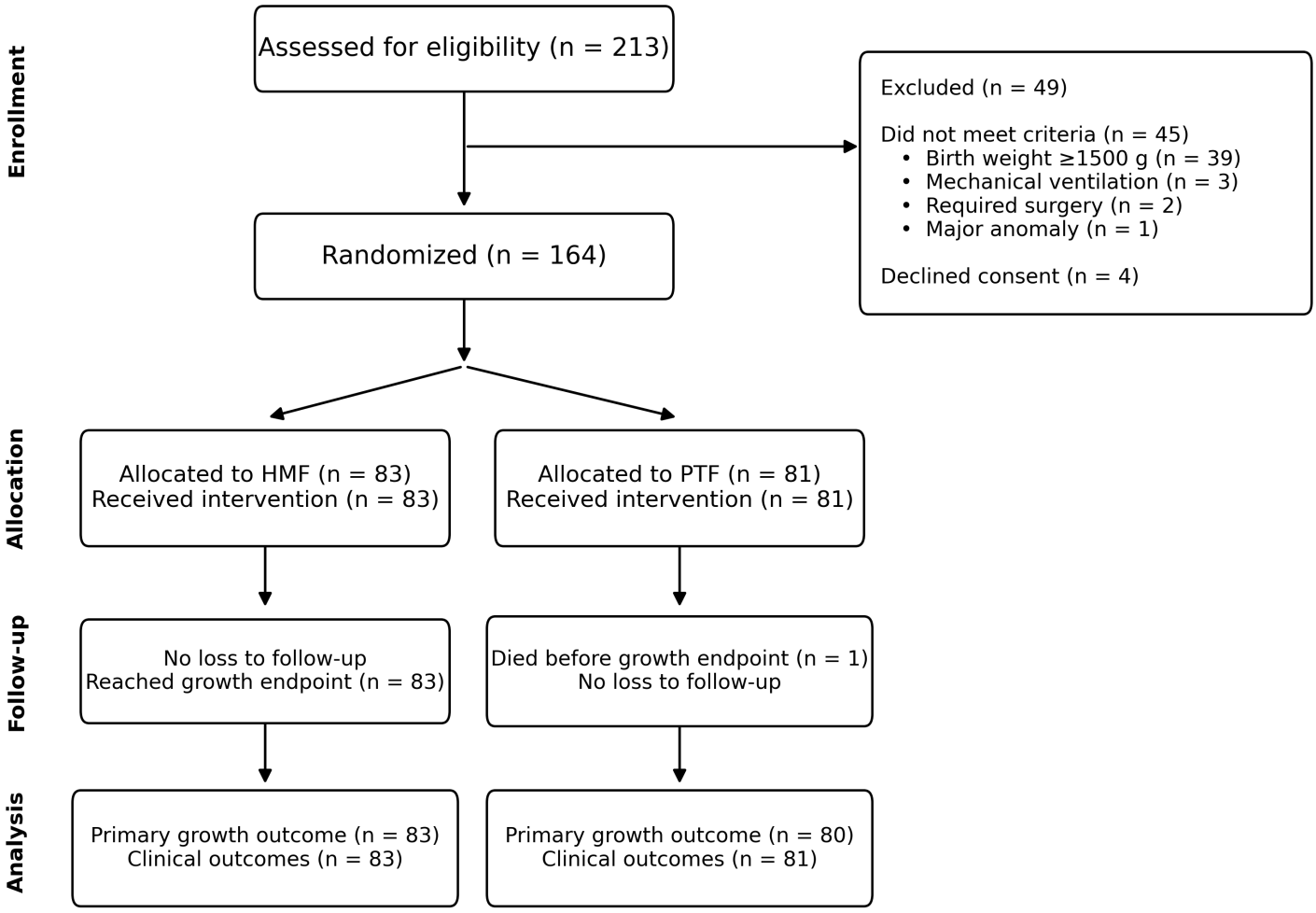


Figure 1

CONSORT flow diagram. One preterm-formula infant died before the primary growth endpoint; the primary growth analysis therefore included 163 infants (HMF 83, PTF 80), and all 164 randomized infants were retained for clinical outcomes.

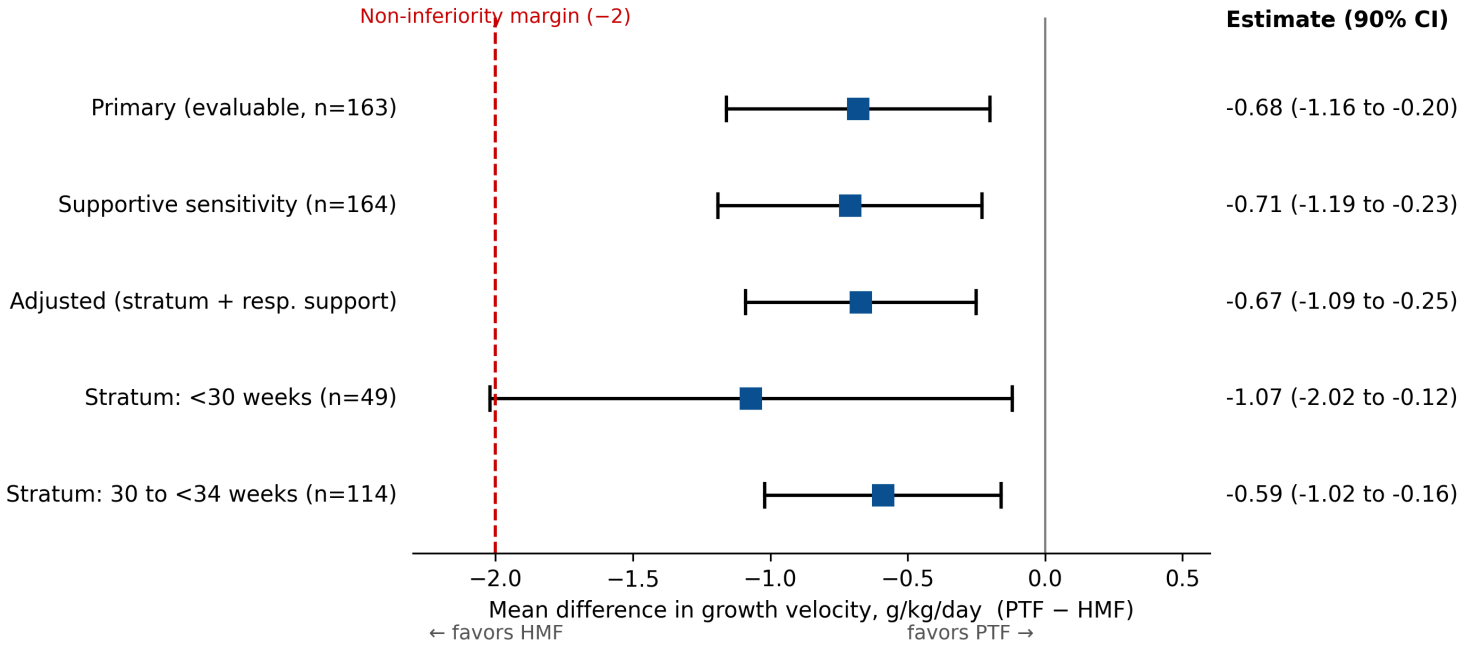


Figure 2

Forest plot of the mean difference (PTF − HMF) in weight growth velocity for the primary (evaluable, n=163), supportive sensitivity (observed growth to the last weight before death, n=164), adjusted, and per-stratum analyses. Points are point estimates and horizontal bars are confidence intervals (90% for the primary, sensitivity, adjusted, and per-stratum non-inferiority estimates). The dashed vertical line indicates the non-inferiority margin (−2 g/kg/day) and the solid line the line of no difference. Per-stratum estimates are descriptive and were not powered as independent non-inferiority comparisons.

Supplementary Files

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