Full exclusively enteral fluids from day 1 versus gradual feeding in preterm infants (FEED1): a open-label, parallel-group, multicentre, randomised, superiority trial

*Shalini Ojha, Eleanor J Mitchell, Mark J Johnson, Chris Gale, William McGuire, Sam Oddie, Sophie S Hall, Garry Meakin, Josie Anderson, Christopher Partlet, Yuanfei Su, Samantha Johnson, Kate F Walker, Reuben Ogollah, Hema Mistry, Seyran Naghdi, Alan Montgomery, Jon Dorling, for the The FEED1 collaborative**

Summary

Background Preterm infants typically receive intravenous fluids or parenteral nutrition while milk feeds are gradually increased. Feeding with milk sooner could reduce length of hospital stay and risk of invasive infections but might increase the risk of necrotising enterocolitis. We aimed to investigate if exclusively enteral fluids (ie, full milk feeds) from day 1 compared with gradual feeding supplemented with intravenous fluids or parenteral nutrition reduces the length of hospital stay in infants born at 30 weeks and 0 days (30⁺⁰ weeks) to 32⁺⁶ weeks of gestation.

Methods This open-label, parallel-group, multicentre, randomised, superiority trial recruited mothers of infants born at 30⁺⁰ weeks to 32⁺⁶ weeks of gestation, in 46 neonatal units in UK hospitals. Infants younger than 3 h were included if they were clinically stable; those with congenital anomalies that make enteral feeding unsafe and who were small for gestational age with reversed end-diastolic flow on umbilical doppler were excluded. Parents and the clinical team could not be masked, but investigators and data analysts were masked until after database lock. The mother was randomly assigned to either full milk feeds (60–80 mL/kg per day) or gradual milk feeding (maximum of 30 mL/kg per day on day 1) with intravenous fluids or parenteral nutrition for their infant within 3 h of birth using a web-based minimisation algorithm with a random element to ensure balance on important prognostic factors. The primary outcome was length of hospital stay; events of hypoglycaemia and necrotising enterocolitis were safety outcomes and analysis was performed by intention-to-treat. This trial was prospectively registered (ISRCTN89654042) and follow-up to 24 months is ongoing.

Findings Between Oct 15, 2019, and July 14, 2024, we recruited and randomly assigned 1761 mothers, enrolling 2088 infants (1047 full milk feeds, 1041 gradual feeding). Mean gestational age was 31·7 weeks (SD 0·8), which was the same in both groups, and mean birthweight was 1626·0 g (301·8) in the full milk feeds group and 1617·1 (295·2) in the gradual feeding group. Of 1047 infants in the full milk group, 494 (47·2%) were female and 552 (52·7%) were male and in 1041 infants in the gradual feeding group, 500 (48·0%) were female and 540 (51·9%) were male. Primary outcome data were missing for 18 infants in each group. We found no difference in the length of hospital stay (32·4 days [SD 13·3] in the full milk group *vs* 32·1 days [13·5] in the gradual feeding group; adjusted difference between means –0·02 days [95% CI –1·07 to 1·03]; p=0·97). Survival to discharge (1030 [99·6%] of 1034 *vs* 1027 [99·6%] of 1031; –0·004 [95% CI –0·54 to 0·53]), presence of necrotising enterocolitis (4 [0·4%] of 1030 *vs* 6 [0·6%] of 1027; –0·19 [–0·80 to 0·41]), and mean number of blood glucose tests <2·2 mmol/L (0·6 [SD 1·0] *vs* 0·5 [0·7]) were similar. Serious adverse events were similar in both groups (eight [0·8%] of 1047 infants in the full milk group *vs* ten [1·0%] of 1041 infants in the gradual feeding group), all were unrelated to trial intervention.

Interpretation In infants born at 30⁺⁰ weeks to 32⁺⁶ weeks of gestation, full milk feeds from day 1 does not alter length of hospital stay. It does not increase the risk of necrotising enterocolitis or hypoglycaemia.

Funding UK National Institute of Health and Care Research.

Lancet Child Adolesc Health 2025; 9: 827–36

Published Online October 17, 2025 https://doi.org/10.1016/S2352-4642(25)00271-8

See Comment page 818

*Collaborators listed in the appendix (pp 15–17)

School of Medicine, University of Nottingham, Nottingham, UK (Prof S Ojha PhD, Prof E J Mitchell PhD, S S Hall PhD, G Meakin BSc, C Partlet PhD, Y Su MSc, Prof K F Walker PhD, R Ogollah PhD, Prof A Montgomery PhD); **Faculty of Medicine, University of Southampton, Southampton, UK** (Prof M J Johnson PhD); **Neonatal Medicine, School of Public Health and Centre for Paediatrics and Child Health, Imperial College London, London, UK** (Prof C Gale PhD); **Centre for Reviews and Dissemination, University of York, York, UK** (Prof W McGuire MD); **Bradford Neonatology, Bradford Royal Infirmary, Bradford, UK** (S Oddie MBBS); **Bliss, London, UK** (J Anderson); **Department of Population Health Sciences, University of Leicester, Leicester, UK** (Prof S Johnson PhD); **Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK** (H Mistry PhD, S Naghdi PhD); **School of Medicine, University of Leeds, Leeds, UK** (Prof J Dorling MD)

Correspondence to: Prof Shalini Ojha, School of Medicine, University of Nottingham, Nottingham NG7 2RD, UK **shalini.ojha@nottingham.ac.uk**

See Online for appendix

Introduction

Infants born preterm or with low birthweight are typically initially given intravenous fluids or parenteral nutrition and milk feeds started at small volumes that are gradually increased until they reach full milk feeds. Although there is no evidence to support it, the common perception that milk feeding too soon or too fast could increase the risk of necrotising enterocolitis has led to cautious approaches to feeding preterm infants.[1] Evidence from randomised trials shows that feeding milk faster could reduce the risk of invasive infections without increasing the risk of necrotising enterocolitis or death.[2] The incidence of necrotising enterocolitis reduces with increasing gestational age such that less than 1% of those born after

Research in context

Evidence before this study

To review the available evidence on full milk feeds from day 1 in preterm infants, we searched MEDLINE from database inception to Aug 5, 2025, without language restriction, using the search terms "infant, preterm*" or "low birth weight or lbw or vlbw" and "early or fast or full feed*". A systematic review (four trials, 436 infants with 1000–1500 g birthweight) found that those who had full milk feeds had a shorter length of hospital stay compared with those gradually fed (median difference −3·07 days [95% CI −4·13 to −2·02]). We found three randomised trials published after the review. Jajoo and colleagues randomly assigned 60 infants with 1000–1499 g birthweight, Razzaghy and colleagues randomly assigned 97 infants born at 28 weeks and 0 days (28^{+0} weeks) to 32^{+6} weeks of gestation within 72 h of birth, and Alsheikh and colleagues randomly assigned 70 infants born at 30^{+0} weeks to 33^{+6} weeks of gestation within 48 h to full milk or gradual feeding. All three studies reported a reduction in length of hospital stay. There was no difference in the risk of necrotising enterocolitis between the two groups in any of the trials. In total, these studies included 617 infants. All but two studies were conducted in single centres in India, one in a single centre in the USA, and one in three centres in Canada. All studies were small and not sufficient to determine if full milk feeding compared with gradual feeding affects important outcomes in preterm infants.

Added value of this study

The FEED1 trial is the largest randomised trial of full milk feeds from day 1 in preterm infants. Full milk feeds from day 1 did not reduce the length of hospital stay and did not affect survival, necrotising enterocolitis, late-onset infections, breastfeeding at discharge, parental satisfaction with neonatal care, and hypoglycaemia. Infants who received full milk feeds from day 1 had one fewer day in intensive care and fewer interventions, including days of intravenous fluids and parenteral nutrition and fewer central and peripheral intravenous lines.

Implications of all the available evidence

Preterm infants born at 30^{+0} weeks to 32^{+6} weeks of gestation can be fed full milk feeds starting soon after birth. Contrary to the findings of other smaller studies, we found that in care settings of the UK National Health Service full milk feeds from birth did not reduce the length of hospital stay, but it appears to be safe and feasible. There was no difference in the risk of necrotising enterocolitis or hypoglycaemia, and there was a reduction in intensive care and interventions such as parenteral nutrition. Feeding protocols for stable infants born at or later than 30^{+0} weeks of gestation can include full milk feeds from birth, considering parental choice about supplementation of own mother's milk in the first few days, if needed.

30 weeks and 0 days (30^{+0} weeks) gestation develop severe necrotising enterocolitis.[3]

Small trials in the past 15 years suggest that in infants born at 1000–1500 g weight, early exclusively enteral fluids (ie, full milk feeds) only without any intravenous fluids or parenteral nutrition such that the infant's full fluid requirements are met with enteral milk feeds) could improve growth and reduce the length of hospital stay[4] compared with delayed or gradual incremental feeds supplemented with intravenous fluids or nutrition. A Cochrane systematic review of infants with 1000–1500 g birthweight found that those who had full milk feeds from day 1 had a shorter length of hospital stay compared with gradual feeding (four studies, 436 infants, median difference −3·07 days [95% CI −4·13 to −2·02]). There was no difference in the risk of necrotising enterocolitis, death, or other adverse events but the number of infants included was small and the evidence was uncertain.[4] All the trials included were single-centre studies conducted in India and it was unclear if the results would be generalisable to high-resource settings, such as the UK.

Feeding an infant sufficient milk to provide all their fluid requirements from birth and incrementing until the infant is receiving full enteral feeds to meet their nutritional requirements would reduce the need for intravenous fluids or parenteral nutrition and the associated placement of venous lines, thus reducing painful procedures and the risk of invasive infections.[5] Feeding preterm infants milk feeds from birth could also improve growth and support infants to become ready for discharge sooner than gradual incremental feeds supplemented with intravenous fluids or nutrition, thus reducing hospital stay.[4] Consultations with parent groups show that going home quickly is important to them. Reduction in the length of stay with reduction in interventions such as use of parenteral nutrition and intravenous fluids would reduce the cost of care for the health service and families.[6] In the Fluids Exclusively Enteral from Day 1 (FEED1) trial, we aimed to find out whether, in infants born at 30^{+0} weeks to 32^{+6} weeks, full milk feeds from day 1 (within 3 h of birth) reduces the length of hospital stay compared with gradual milk feeding with supplemental intravenous fluids or parenteral nutrition.

Methods

Study design

FEED1 was an open-label, parallel-group, multicentre, randomised, superiority trial of full milk feeds from day 1 (within 3 h of birth) versus gradual feeding with supplemental intravenous fluids or parenteral nutrition in infants born at 30^{+0} weeks to 32^{+6} weeks. Recruitment was from 46 neonatal units in UK National Health Service hospitals across England, Scotland, and Wales. The trial

was approved by the East Midlands Derby Research Ethics Committee (19/EM/0258) and the protocol published.[6] The statistical analysis plan is available online.[7] The study was prospectively registered (ISRCTN89654042) and follow-up to 24 months is ongoing.

We developed and delivered the FEED1 trial in collaboration with Bliss, the organisation for families of infants born preterm and sick. We had input from parent representatives in the development of the trial protocol, acquisition of funding, developing and reviewing documents, trial delivery, monitoring, and interpretation and writing of the results. We will work with parents in further dissemination of the results.

Participants

Women were approached antenatally if they were expected to deliver at 30^{+0} weeks to 32^{+6} weeks or after the infant had been born if preterm birth was not anticipated. Mothers gave oral assent or written informed consent before randomisation. Mothers who had given oral assent later gave full written informed consent for continued participation and data collection. We included infants who were born at 30^{+0} weeks to 32^{+6} weeks of gestation and were younger than 3 h (180 min) at time of study enrolment. We excluded infants with known congenital abnormalities of the gastrointestinal tract or other congenital conditions that make enteral feeding unsafe; infants who were small for gestational age (SGA; defined as birthweight less than 10th centile) and had reversed end-diastolic flow on antenatal umbilical artery doppler ultrasonography; and if the mother had participated in the trial during a previous pregnancy. Umbilical artery doppler ultrasonography was not performed routinely; infants were excluded if a clinically indicated examination met the exclusion criteria. Infants with absent end-diastolic flow were not excluded, and those with reversed end-diastolic flow were excluded only if they were SGA. Eligible infants were assessed by the attending neonatal clinician and enrolled if deemed clinically stable as per their judgement. Infants requiring respiratory support (eg, via continuous positive airway pressure or mechanical ventilation) or other supportive treatments were included if the attending clinician was in equipoise about the infant being randomly assigned to either the full milk or the gradual milk group. Sex of the baby was determined as recorded in clinical notes (determined by clinical examination at birth) and ethnicity was self-reported by the mother.

Randomisation and masking

The mother was randomly assigned to either the full milk group or the gradual milk group to ensure that infants from a multiple pregnancy would be randomly assigned to the same group; parents and public partners told us they would not like to feed their infants differently. Mothers were randomly assigned (1:1) via a secure web-based system developed and maintained by the Nottingham Clinical Trials Unit to ensure allocation concealment. Randomisation used a minimisation algorithm with a random element to ensure balance on important prognostic factors: site, single or multiple birth, gestation (in weeks) at birth, SGA, and whether intravenous fluids were started before randomisation. We could not mask parents or the clinical team to the intervention, but investigators and data analysts were masked until after database lock. Any event of unblinding of investigators and data analysts was reported if they occurred, none were reported.

Procedures

For infants in the full milk group, we started milk feeds within 3 h of birth at 60–80 mL/kg per day via a gastric tube and continued milk feeds without intravenous fluids or parenteral nutrition. For those in the gradual feeding group, we started intravenous fluids or parenteral nutrition and small volumes of milk feeds (maximum of 30 mL/kg per day on day 1) according to local standard practice. Across both groups, all other care was according to local practice, such as feeding intervals, feed volume increments, type of milk (formula or human donor milk) for supplementing the mother's milk if insufficient, and the definition of feed intolerance, including the decision to interrupt or stop milk feeds.

We collected primary outcome data at hospital discharge. We collected data on daily intravenous fluid or parenteral nutrition and milk feed volumes, type of milk (own mother's milk, donor human milk, or formula), and any measured blood glucose values until the infant reached full enteral feeds, defined as at least 140 mL/kg per day sustained for 3 consecutive days. We collected the incidence of necrotising enterocolitis and late-onset sepsis throughout neonatal care and other secondary outcomes at hospital discharge.

We defined adherence to allocation as 24 h or less of intravenous fluids or parenteral nutrition from birth until reaching full enteral feeds for the full milk group and as more than 24 h of intravenous fluids or parenteral nutrition from birth to reach full enteral feeds in the gradual feeding group. We permitted change from the allocated treatment if the infant was unable to tolerate the allocated feeding regimen in the opinion of the attending clinician and recorded this reasoning. We also collected additional maternal and infant outcomes by electronic or postal questionnaire, supplemented by telephone interviews, when the infant was aged 6 weeks corrected for preterm birth.

Outcomes

The primary outcome was length of hospital stay, which included the total duration in any neonatal unit measured from day of birth to the day of discharge home. The trial design was pragmatic and hospitals could apply different discharge criteria. We analysed a secondary outcome of time until objective discharge

criteria were met, defined as the age at which the infant met all three criteria: current weight at least 1700 g, ability to take at least one full suck feed assessed as adequate, and not receiving additional temperature support for at least 24 h.

Key secondary outcomes were survival, incidence of necrotising enterocolitis (defined as Bell's stage 2 or 3), incidence of microbiologically confirmed or clinically suspected late-onset sepsis, hypoglycaemia, and breast-feeding own mother's milk up to hospital discharge. Classification of necrotising enterocolitis and late-onset sepsis were confirmed by a masked endpoint review committee using standard definitions[2] if outcomes were ambiguous. Definitions of all secondary outcomes are

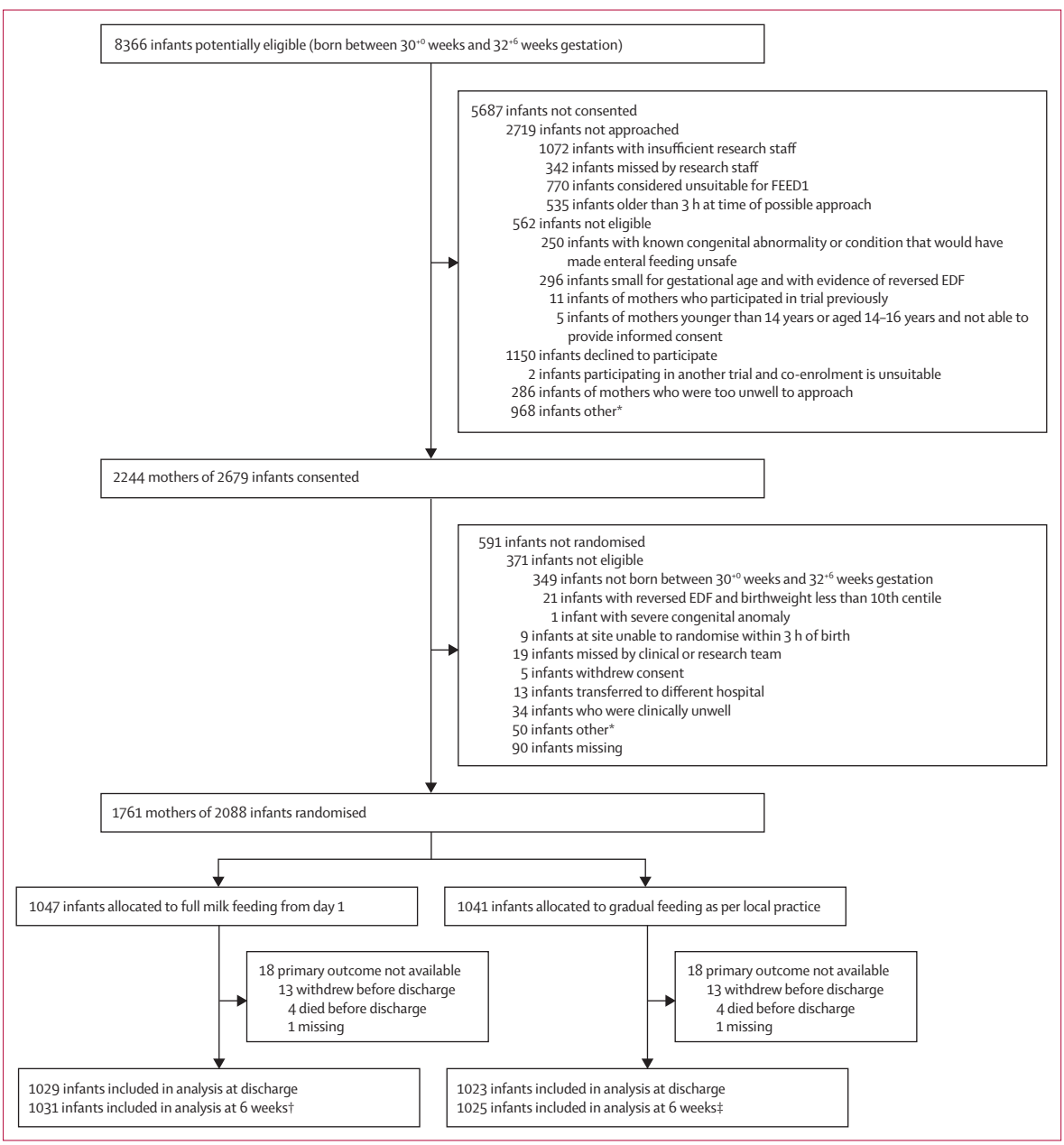

Figure 1: **Trial profile**

Infants included in the primary analysis were those who survived, were discharged, and whose mothers had not withdrawn consent. Infants included in the 6-week analysis were those who survived to 6 weeks corrected age and whose mothers had not withdrawn consent. EDF=end-diastolic flow. *Other reasons are listed in the appendix (p 17). †Two infants in the full milk group survived to 6 weeks corrected age but died before discharge or had missing data on the primary outcome, and were therefore included in the 6 week analysis but not the discharge analysis. ‡Three infants in the gradual feeding group survived to 6 weeks corrected age so were included in the 6 week analysis but died before discharge or had missing data on the primary outcome, and were therefore not included in the primary analysis; one infant was discharged but died before 6 weeks corrected age and was included in the discharge analysis.

given in the appendix (p 1). We compared the number of adverse events and serious adverse events by trial group. The data monitoring committee monitored necrotising enterocolitis and hypoglycaemia as safety outcomes. We report the within-trial economic evaluation up to age 6 weeks corrected for preterm birth separately. The results of the ongoing study up to age 24 months corrected for preterm birth and the long-term health economic evaluation will be reported later.

Statistical analyses

Previous data[8] suggest that the length of hospital stay for our population ranges from 20 to 40 days (SD 9–16). Using a SD of 13, we estimated that 1778 infants would detect a between group difference in means of 2 days with 90% power, 1:1 allocation, and 5% two-sided significance. From previous trials,[2] we expected 15% of pregnancies to be twins and 1·4% of pregnancies to be triplets, with an intracluster correlation coefficient for multiple pregnancy to be 0·82, requiring a sample size inflation of 15%. We further inflated the sample size by 2% for non-collection of primary outcome data, giving a sample size of 2088 infants.

Baseline demographic and clinical characteristics were summarised with counts and percentages for categorical variables and means and SDs or median and lower and upper quartiles for continuous variables. All outcomes were analysed in the group to which infants were randomly allocated (intention-to-treat), except for those whose mothers withdrew consent. Infants who died before discharge were not included in the analysis of the primary outcome but were included in other outcome analyses.

Outcomes were analysed using mixed-effects regression models that took account of the hierarchical data structure by including random effects for mothers and research sites, and fixed effects to adjust for minimisation variables. We used linear models for continuous outcomes, logistic models for binary outcomes, or Cox regression models for time-to-event outcomes to estimate between-group effects and 95% CI. Risk differences between groups were obtained using Stata's margins command with SEs computed using the delta method.[9] Estimated parameters from the margins command were applied to compute risk ratios. SGA and whether intravenous fluids were started before randomisation were included as binary variables, and completed weeks of gestation at birth was included as a categorical variable.

Subgroup analyses for the primary outcome and key secondary outcomes (necrotising enterocolitis and late-onset sepsis) were prespecified for completed weeks of gestation at birth and SGA and conducted by including interaction terms in the primary model. A sensitivity analysis using missing value imputation for the primary outcome was not conducted as planned due to the low number of missing primary outcome data.

	Full milk (n=1047)	Gradual feeding (n=1041)
Infant sex		
Male	552 (52·7%)	540 (51·9%)
Female	494 (47·2%)	500 (48·0%)
Indeterminate	1 (0·1%)	1 (0·1%)
Infant age at randomisation (h)	1·7 (0·8)	1·7 (0·8)
Gestational age at birth (weeks)	31·7 (0·8)	31·7 (0·8)
30⁺⁰ to 30⁺⁶	229 (21·9%)	233 (22·4%)
31⁺⁰ to 31⁺⁶	348 (33·2%)	345 (33·1%)
32⁺⁰ to 32⁺⁶	470 (44·9%)	463 (44·5%)
Birthweight (g)	1626·0 (301·8)	1617·1 (295·2)
<1000 g	9 (0·9%)	11 (1·1%)
≥1000 g to <1500 g	354 (33·8%)	350 (33·6%)
≥1500 g to <2000 g	562 (53·7%)	584 (56·1%)
≥2000 g	122 (11·7%)	96 (9·2%)
Small for gestational age (birthweight <10th centile)	126 (12·0%)	116 (11·1%)
Intravenous fluids started before randomisation	531 (50·7%)	534 (51·3%)
Infant heart rate >100 beats per min at 5 min	983/1032 (95·3%)	981/1028 (95·4%)
Infant temperature on admission (°C)	36·9 (0·5)*	36·9 (0·4)†
Infant worst base excess within first 24 h of birth (mmol/L)	−3·7 (4·0)‡	−3·5 (3·7)§
Infant receiving respiratory support at time of randomisation¶	831/1034 (80·4%)	821/1032 (79·6%)
Mechanical ventilation	50/831 (6·0%)	62/821 (7·6%)
Continuous positive airway pressure	598/831 (72·0%)	594/821 (72·4%)
High flow oxygen	169/831 (20·3%)	154/821 (18·8%)
Any other supplemental oxygen	45/831 (5·4%)	42/821 (5·1%)
Reversed end diastolic flow on maternal doppler	10 (1·0%)	11 (1·1%)
Multiple pregnancy	331 (31·6%)	325 (31·2%)
Mother's age at randomisation (years)	31·7 (6·2)	32·1 (6·0)
Mother's ethnicity		
White	743/1043 (71·2%)	753/1036 (72·7%)
Mixed	24/1043 (2·3%)	15/1036 (1·4%)
Asian or Asian British	138/1043 (13·2%)	129/1036 (12·5%)
Black or Black British	74/1043 (7·1%)	70/1036 (6·8%)
Other	21/1043 (2·0%)	26/1036 (2·5%)
Not stated	43/1043 (4·1%)	43/1036 (4·2%)
Mother received antenatal corticosteroids	938/1043 (89·9%)	947/1036 (91·4%)
Mother received magnesium sulfate	702/1043 (67·3%)	701/1036 (67·7%)
Caesarean section	739/1034 (71·5%)	735/1032 (71·2%)
Amniotic membranes ruptured >24 h before birth	236/1033 (22·8%)	232/1026 (22·6%)

Data are n (%), mean (SD), or n/N (%). Patient numbers are shown if there were missing data. 30⁺⁰=30 weeks *n=1034. †n=1032. ‡n=1021. §n=1015. ¶Types of respiratory support includes all forms of respiratory support received before randomisation; an infant can have received more than one type of respiratory support.

Table 1: **Baseline characteristics**

Exploratory non-randomised analyses, as detailed in the statistical analysis plan,[7] were planned to assess differences between infants who received formula milk and those who received donor human milk as supplementation to own mother's breastmilk. These analyses were planned due to concerns that full milk feeding from day 1 would require mother's milk to be

supplemented as most mothers are unlikely to produce sufficient volumes on day 1 and the need for supplementation could affect outcomes.

The independent data monitoring committee and independent trial steering committee reviewed summary data, offered guidance, and identified data quality issues based on reports generated by the masked trial statistician. All analyses were performed using Stata version 18.0.

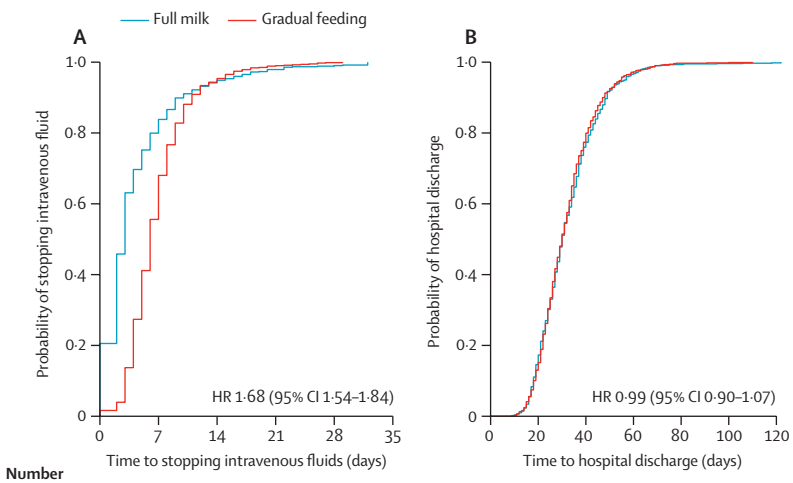

Figure 2: **Kaplan–Meier curves for time (days from birth) to intravenous fluids or parenteral nutrition being stopped and discharge from neonatal care**
HR=hazard ratio.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or report writing.

Results

Between Oct 15, 2019, and July 14, 2024, we identified 8366 infants born at 30⁺⁰ weeks to 32⁺⁶ weeks of gestation in 46 neonatal units across England, Scotland, and Wales (appendix p 3). Participant flow is described in figure 1 and baseline characteristics in table 1 and the appendix (p 4). Of 2088 infants enrolled, mean gestational age was 31·7 weeks (SD 0·8), mean birthweight was 1621 g (SD 298), 994 (47·6%) were female, 1092 (52·3%) were male, and the mean age at randomisation was 1·7 h (SD 0·8). Overall, 1432 (68·6%) were singletons, 242 (11·6%) were SGA, and 21 (1%) had evidence of reversed end-diastolic flow on antenatal umbilical doppler scan.

Of 1047 infants in the full milk group, 214 (20·4%) were fully milk fed from birth and did not receive any intravenous fluid or parenteral nutrition. In this group, 644 (61·5%) infants received no or 24 h or less of intravenous fluids or parenteral nutrition. In 1047 infants, the reason for non-adherence to full milk feeds was reported for 387 (37·0%) infants:

	Full milk (n=1047)	Gradual feeding (n=1041)	Adjusted risk difference (95% CI)	Adjusted risk ratio (95% CI)	Adjusted hazard ratio (95% CI)	Adjusted difference in counts* (95% CI)
Survived to discharge	1030/1034 (99·6%)	1027/1031 (99·6%)	−0·004 (−0·54 to 0·53)	1·00 (0·99 to 1·01)	..	..
Microbiologically confirmed or clinically suspected late-onset sepsis before discharge	32/1031 (3·1%)	25/1026 (2·4%)	0·66 (−0·75 to 2·07)	1·27 (0·76 to 2·13)	..	..
Necrotising enterocolitis (Bell stage 2 or 3) before discharge	4/1030 (0·4%)	6/1027 (0·6%)	−0·19 (−0·80 to 0·41)	0·67 (0·19 to 2·35)	..	..
Any breastfeeding at discharge	447/1026 (43·6%)	434/1021 (42·5%)	1·51 (−2·47 to 5·49)	1·04 (0·94 to 1·14)	..	..
Exclusive breastmilk fed at discharge	109/1026 (10·6%)	117/1021 (11·5%)	−0·60 (−3·23 to 2·03)	0·95 (0·74 to 1·20)	..	..
Survived to 6 weeks	1031/1034 (99·7%)	1027/1031 (99·6%)	0·09 (−0·41 to 0·60)	1·00 (1·00 to 1·01)	..	..
Breastfeeding at 6 weeks	301/697 (43·2%)	276/657 (42·0%)	..	..	..	..
Mother's breastmilk fed at 6 weeks	370/693 (53·4%)	314/642 (48·9%)	..	..	..	..
Time to objective discharge criteria met (days)	23·2 (10·7), n=1010	23 (10·7), n=1010	..	..	1·07 (0·89 to 1·29)	..
Time to full enteral feeds (days)	7·0 (3·5)	7·9 (3·9)	..	..	2·35 (1·91 to 2·89)	..
Parenteral nutrition until discharge (days)	1·1 (3·4); n=1029	2·7 (7·2); n=1022	..	..	..	−1·52 (−1·98 to −1·06)
Number of central venous lines inserted until discharge	0·2 (0·8), n=1029	0·4 (1·0), n=1022	..	..	..	−0·16 (−0·23 to −0·08)
Time with central line until discharge (days)	1·0 (3·4), n=1029	2·1 (7·0), n=1022	..	..	..	−0·87 (−1·31 to −0·42)
Peripheral cannula until full milk feeding (days)	4·3 (3·0), n=1019	5·3 (2·9), n=1015	..	..	..	−1·4 (−1·29 to −0·78)
Number of intravenous cannulae inserted until full milk feeding	1·6 (1·4), n=1019	2·1 (1·8), n=1015	..	..	..	−0·52 (−0·66 to −0·38)
Number of glucose tests <2·2 mmol/L until full feeds	0·6 (1·0), n=1019	0·5 (0·7), n=1015	..	..	..	..

Data are n/N (%) or mean (SD), unless otherwise indicated. Patient numbers are shown if there were missing data. *Adjusted difference in counts was estimated with a zero-inflated negative binomial model adjusting for minimisation factors, with length of hospital stay as the inflation factor.

Table 2: **Secondary outcomes**

130 (12·4%) did not tolerate milk feeds (vomiting or large gastric aspirates); 27 (2·6%) had abdominal concerns including suspected necrotising enterocolitis; 68 (6·5%) had hypoglycaemia; 5 (0·5 %) changed due to parental choice; 74 (7·1%) had feeds interrupted due to need for escalation of respiratory support; and 83 (7·9%) had other reasons (appendix p 7). Two (0·2%) of 1047 infants were reported as adherent but feeding data suggested they had more than 24 h of intravenous fluids and 14 (1·3%) of 1047 infants had incomplete feeding logs (appendix p 7). In 1042 infants in the gradual feeding group 947 (91·0%) were adherent and received more than 24 hours of intravenous fluids or parenteral nutrition (appendix p 7). The median duration of intravenous fluids or parenteral nutrition was shorter in the full milk group compared with the gradual feeding group (figure 2; median duration 14 h [IQR 55] in the full milk group and 99 h [87] in the gradual feeding group; appendix p 6). The median volume of milk feeds received on day 1 was 38 mL/kg (IQR 37) in the full milk group and 1 mL/kg (12) in the gradual feeding group. The volume received on days 2, 3, and 4 is given in the appendix by allocated group (p 7).

Primary outcome data were not available for 36 (1·7%) of 2088 infants. There was no difference in the primary outcome, length of hospital stay (mean 32·4 days [SD 13·3] *vs* 32·1 days [13·5]; adjusted difference between means –0·02 days [95% CI –1·07 to 1·03]; p=0·97), between the two groups (figure 2).

For the key secondary outcomes, there was no difference in survival to discharge, late-onset sepsis, necrotising enterocolitis, hypoglycaemia, or breastfeeding at discharge or at age 6 weeks corrected for preterm birth (table 2). Infants in the full milk group reached full enteral feeds sooner, had shorter duration of parenteral nutrition and intravenous fluids, fewer central and peripheral intravenous lines, and fewer days with central and intravenous lines in situ (table 2). The mean day on which infants met all three criteria objective discharge criteria was similar (table 2) and there was no difference in the time to regain birthweight or weight Z score adjusted for gestational age at discharge (appendix p 9). Infants in the full milk group received fewer days of intensive care and more special care days (appendix p 10).

There were no differences in the primary or key secondary outcomes by gestational age (weeks at birth) or SGA in the subgroup analyses (figure 3 and appendix p 10). The mean length of stay for the subgroup of 242 SGA infants was 36·7 days (SD 11·9) for the full milk group and 39·0 days (21·1) for those in the gradual feeding group but adjusted mean difference was not statistically significant. No SGA infant in the full milk group had Bell stage 2 or 3 necrotising enterocolitis.

Similar numbers of serious adverse events were reported in both groups (eight [0·8%] of 1047 infants in the full milk group *vs* ten [1·0%] of 1041 infants in the gradual feeding group), all were unrelated to trial intervention (appendix p 11). As expected, infants in the full milk group received larger volumes of human donor milk or formula milk compared with those in the gradual feeding group. Results of the exploratory analyses are given in the appendix (pp 12–15).

Discussion

In infants born at 30^{+0} weeks to 32^{+6} weeks, full milk feeds from day 1 did not reduce the length of hospital stay compared with intravenous fluids or parenteral nutrition with gradual feeding. The trial involved 46 hospitals that have variations in discharge policies that determine length of hospital stay. Therefore, we also measured time to physiological readiness for discharge, which was the same in both groups. Length of stay is

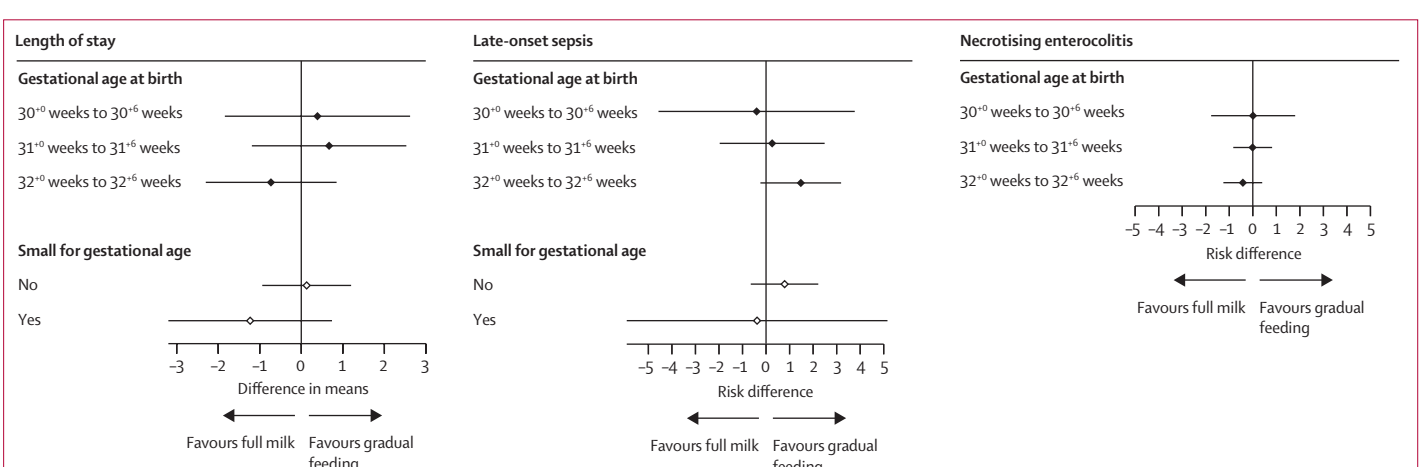

Figure 3: **Subgroup analyses**
The total difference in means for length of hospital stay was –0·02 (95% CI –1·07 to 1·03). The total risk differences for microbiologically confirmed or clinically suspected late-onset sepsis was 0·66 (95% CI –0·75 to 2·07) and necrotising enterocolitis (Bell stage 2 or 3) was –0·19 (95% CI –0·80 to 0·41). Subgroup analysis on the effect of small for gestational age on necrotising enterocolitis was not performed due to multicollinearity. No infant in the small for gestational age subgroup who was in the full milk group had necrotising enterocolitis.

dependent on gestational age at birth and has been shown to be 36 days on average for infants born at 30 and 31 weeks of gestation.[10] In the FEED1 trial, infants met the physiological discharge readiness criteria by day 23 on average, but remained in hospital until day 32. Infants were enrolled only when attending clinicians were in equipoise about full milk versus gradual feeding, and infants who were unwell at birth might not have been considered for enrolment. Thus, there could have been a selection of those at lower risk of complications who then required a shorter hospital stay compared with the overall population at these gestational ages.

We did not find an increased risk of adverse events including necrotising enterocolitis and hypoglycaemia, and supplementing mother's milk to enable full milk feeding from day 1 did not affect breastfeeding rates at discharge or at age 6 weeks corrected for preterm birth. Infants were allocated a feeding group within 3 h of birth so that full milk feeding could be started, if possible, with minimal need for intravenous nutrition. With this protocol, almost two-thirds of those randomised to full milk received less than 24 h of intravenous nutrition, including one in five infants who did not receive any intravenous fluids or parenteral nutrition. Overall, infants in the full milk group reached full milk feeds at a median of 14 h compared with 99 h in infants allocated gradual feeding. Infants in the full milk group had a shorter duration of parenteral nutrition, the time with an indwelling central or peripheral intravenous line was shorter, and they had one fewer day of intensive care but spent one day longer in special care compared with infants who were gradually fed. These differences could have important resource implications. Within-trial economic evaluation will be reported separately.

Contrary to our results, the meta-analysis in the Cochrane systematic review[4] found that full milk feeds from day 1 reduces length of hospital stay compared with gradual feeding. However, all included studies were single-centre studies from India.[11,12] The reported lengths of stay were shorter than those reported for similar infants in the UK,[10] which might be due to the differences in health-care delivery. In addition, there was significant statistical heterogeneity in the meta-analyses due to the small number of infants and results were imprecise with few cases of necrotising enterocolitis and other adverse outcomes reported. The evidence was, therefore, graded as low certainty. Since then, one further single-centre study from India by Jajoo and colleagues[13] of 60 infants with birthweight 1000–1499 g has also reported a shorter length of hospital stay in the full milk group compared with the gradual feeding group.

Since 2023, studies of early full enteral nutrition similar to the FEED1 intervention have been reported from North America. Alsheikh and colleagues randomly assigned 70 infants born at 30^{+0} weeks to 33^{+6} weeks of gestation to full feeds within 48 h or gradual feeding in a three-centre study in Canada and reported a large reduction in length of hospital stay in the full milk group (mean difference –6·6 days [IQR –12·9 to –0·2]).[14] The length of stay for the full milk group in this trial (mean 31·5 [SD 12·9]) was similar to both groups of FEED1 infants, whereas the stay for gradually fed infants was much longer (39·5 [16·4]) than both groups of FEED1 infants. Razzaghy and colleagues randomly assigned 97 infants born at 28^{+0} weeks to 32^{+6} weeks of gestation to receiving full milk or gradual feeding within 72 h of birth. They reported that the mean length of stay was 40 days (SD 18) in the full milk group and 47 days (21) in the gradual feeding group.[15] The infants in the full milk group were larger and more mature than those in the gradual feeding group and after adjusting for these baseline differences, the length of stay was not different. Unlike in FEED1, these two trials did not aim to fully milk feed the infants on day 1. The gestational ages included in these trials also differed, but the gestational ages included in FEED1 overlapped with those included in both trials.

Compared with infants in the gradual feeding group, we found that the infants in the full milk group were successfully fed more milk in the first 4 days and reached full enteral feeds sooner, with fewer intravenous cannulations, central lines, and days of intravenous fluids or parenteral nutrition, which explains why the infants in this group moved out of intensive care sooner. This improvement was reached without any increased risk of necrotising enterocolitis or other adverse outcomes. Previous studies had similar findings: Razzaghy and colleagues[15] reported one case of necrotising enterocolitis in each group and there were no cases of necrotising enterocolitis reported by Alsheikh and colleagues.[14] Studies from India also did not find any increase in risk of necrotising enterocolitis. We expected that with full milk feeds from day 1 infants would have fewer central line days, which would reduce the risk of late-onset sepsis, compared with gradual feeding. However, there was no difference in the risk of late-onset sepsis, possibly because both groups had short times with central lines in place and the incidence of infections was low in both groups.

In the prespecified subgroup analysis we found, as expected, a decreasing length of stay with increasing gestational age at birth but no difference between the feeding groups. Similarly, there were no differences in the key secondary outcomes, including necrotising enterocolitis and sepsis. The second prespecified subgroup analysis showed that the length of stay was 37 days for SGA infants in the full milk group and 39 days in the gradual feeding group, but there were only 242 infants in this analysis and the comparison was underpowered to detect a significant difference. Reassuringly, there were no cases of necrotising enterocolitis in the SGA infants who were in the full milk group.

We also performed a prespecified exploratory analysis of the type of milk used to supplement own mother's milk for infants if the mother's milk volumes were not sufficient to meet the infant's requirements. Infants in the full milk group received higher volumes of both human donor milk and formula because they had larger volumes of milk than infants in the gradual feeding group on the first few days. Reassuringly, both groups had similar rates of breastfeeding. These data show that early full milk feeds with supplementation while the mother's milk supply is being established does not adversely affect the chances of the infant breastfeeding at or after discharge home.

In addition to examining necrotising enterocolitis for the safety analysis, we recorded the blood glucose concentrations when blood glucose was measured for clinical indication. Infants in both groups had similar numbers of blood glucose measurements and there was no difference in the proportion of infants with blood glucose concentrations less than 2·2 mmol/L or 1·0 mmol/L.

The main reason for not adhering to full milk feeds from day 1 was the clinical impression that the infant was not tolerating feeds, as suggested by large gastric aspirates, abdominal distention, or vomiting. In addition, 7·1% of infants had their feeds reduced or stopped due to the need for additional respiratory support. As this was a pragmatic trial, attending clinicians could decide when to reduce or stop feeding for clinical reasons. For generalisability of the results, we did not mandate detailed feeding protocols and definition of feed intolerance. Although this could have introduced variations by trial site in how infants were treated, it ensured that clinicians and parents were able to make decisions as per the infant's clinical condition whenever required. Another limitation was that it was not feasible to mandate discharge criteria; therefore, there were variations in discharge practices, which would have affected the primary outcome. To mitigate these variations in practices, particularly those related to feeding and discharge, we minimised randomisation by site and adjusted the analyses for this variable. This limitation was noteworthy because the trial intervention could not be masked, so we assessed a more objective measure of discharge readiness as a secondary outcome but did not find an effect of intervention on this outcome either.

The main strength of the FEED1 trial was successful recruitment and randomisation of infants within 3 h of birth. The mean age at randomisation was 1·7 h, enabling full milk feeds to be started soon after birth. We used a two-stage consent pathway that allowed antenatal written consent or oral assent followed by deferred written consent to enable randomisation within 3 h of birth.[16] We randomly assigned the mother to avoid delays and to allow infants from multiple pregnancies to be fed in the same way, as directed by our parent and public consultations and in keeping with previous feeding trials.[2] Only 26 (1·3%) of 2088 infants were withdrawn after randomisation as their mother did not give consent for continued participation and data collection after receiving full explanation. Including deaths before discharge, primary outcome data were not available for 36 (1·7%) of 2088 infants, which was less than the 2% accounted for in the sample size estimation. Another strength is that we followed up infants after discharge home. Any intervention that could expedite discharge is truly effective only if the infants remain well and do not require readmission.[17] No previous trial has had any post-trial follow-up. We have reported outcomes up to age 6 weeks corrected for preterm birth and we are conducting post-trial follow-up to assess survival without neurodevelopmental disability at age 24 months corrected for preterm birth. Also, we have conducted a formal health economics evaluation, the results of which will be presented separately.

FEED1 is the only adequately powered trial to investigate the effect of full milk feeding from day 1 on length of stay and other important clinical outcomes in preterm infants. The trial was conducted across 46 neonatal units in England, Scotland, and Wales, with a pragmatic but robustly implemented protocol and the results are therefore more generalisable than those of smaller studies.

Although conducted in the UK, these results apply to the worldwide population of similar infants, most of whom are cared for in low-income and middle-income countries. Addition of these results strengthens the evidence that although length of hospital stay might not be reduced in all care settings, stable infants born at 30^{+0} weeks to 32^{+6} weeks of gestation can be fully milk fed from birth without any adverse effect on outcomes at hospital discharge or at age 6 weeks corrected for preterm birth. Infants with SGA were included except those who had reversed end-diastolic flow on umbilical doppler. Further research should aim to explore optimal feeding interventions for infants born at or later than 30 weeks of gestation who do not tolerate full milk feeds from day 1 and full milk feeding from day 1 in small (<1000 g birthweight) and infants born before 30 weeks of gestation.

Contributors

SOj is the Chief Investigator of the study, had overall responsibility for the study, and contributed to conceptualisation, funding acquisition, investigation, methodology, project administration, and writing (original draft, reviewing, and editing). JD was the co-lead of the project, contributed to conceptualisation, led funding acquisition, and contributed to methodology, project administration, and writing (reviewing and editing). YS directly accessed and verified the data and performed data curation, formal data analysis, data visualisation, and writing of the original draft. RO and CP also directly accessed and verified the data and led on data curation, formal analysis, investigation, software, visualisation, and writing (reviewing and editing). EJM, RO, MJJ, CG, WM, SOd, SJ, KFW, HM, GM, JA, and AM contributed to funding acquisition, methodology, project administration, supervision, and writing (reviewing and editing). SN contributed to the health economics and supported the writing (reviewing and editing). SSH contributed to project administration, supervision, and writing (reviewing and editing). All authors had full access to all the data in the study, contributed to draft

versions of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The study protocol is in the appendix and the statistical analysis plan is available online (https://www.feed1.ac.uk/documents/newsletters/feed1-statistical-analysis-plan-final-v2.0-03feb2025.pdf). De-identified individual participant data that underlie the results reported in this Article will be made available for the purpose of an individual participant data meta-analysis to researchers whose proposed use of the data has been approved. Datasets containing individual participant data are available upon reasonable request by email to the corresponding author or ctu@nottingham.ac.uk, a minimum of 6 months after publication of this Article. Access to the data will be subject to review of a data sharing and use request committee including the Chief Investigator and trial sponsor and will only be granted upon receipt of a data sharing and use agreement. Any data shared will be anonymised, which could affect the reproducibility of published analyses.

Acknowledgments

The trial was funded by the National Institute of Health and Care Research Health Technology Assessment Programme (HTA17/94/31) and sponsored by the University Hospitals of Derby and Burton National Health Service Foundation Trust. We thank all the infants and their families who participated in the study, the research nurses, doctors, nurses, and allied care professionals at the participating sites, research team at the Nottingham Clinical Trials Unit, the East Midlands Regional Research Delivery Network, and the UKAMB. We would also like to thank Charlotte Wroughton, other parent and public partners, and the charity Bliss for their advice.

References

1 Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database Syst Rev* 2021; **8:** CD001241.
2 Dorling J, Abbott J, Berrington J, et al, and the SIFT Investigators Group. Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants. *N Engl J Med* 2019; **381:** 1434–43.
3 Battersby C, Longford N, Mandalia S, Costeloe K, Modi N, and the UK Neonatal Collaborative Necrotising Enterocolitis (UKNC-NEC) study group. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study. *Lancet Gastroenterol Hepatol* 2017; **2:** 43–51.
4 Walsh V, Brown JVE, Copperthwaite BR, Oddie SJ, McGuire W. Early full enteral feeding for preterm or low birth weight infants. *Cochrane Database Syst Rev* 2020; **12:** CD013542.
5 Salas AA, Ojha S. Exclusive enteral nutrition in preterm infants: How early is too early? *Semin Fetal Neonatal Med* 2025; **30:** 101631.
6 Mitchell EJ, Meakin G, Anderson J, et al. The FEED1 trial: protocol for a randomised controlled trial of full milk feeds versus intravenous fluids with gradual feeding for preterm infants (30–33 weeks gestational age). *Trials* 2022; **23:** 64.
7 Su Y, Partlett C, Ogollah R, Ojha S, Stenson B. FEED1: statistical analysis plan. April 23, 2023. https://www.feed1.ac.uk/documents/newsletters/feed1-statistical-analysis-plan-final-v2.0-03feb2025.pdf (accessed July 7, 2025).
8 Kwok TC, Dorling J, Ojha S. Multicentre prospective observational study of feeding practices in 30-33 weeks preterm infants. *BMJ Paediatr Open* 2017; **1:** e000040.
9 Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in Stata. *Stata J* 2013; **13:** 492–509.
10 Seaton SE, Barker L, Draper ES, Abrams KR, Modi N, Manktelow BN, and the UK Neonatal Collaborative. Estimating neonatal length of stay for babies born very preterm. *Arch Dis Child Fetal Neonatal Ed* 2019; **104:** F182–86.
11 Sanghvi KP, Joshi P, Nabi F, Kabra N. Feasibility of exclusive enteral feeds from birth in VLBW infants >1200 g—an RCT. *Acta Paediatr* 2013; **102:** e299–304.
12 Nangia S, Bishnoi A, Goel A, Mandal P, Tiwari S, Saili A. Early total enteral feeding in stable very low birth weight infants: a before and after study. *J Trop Pediatr* 2018; **64:** 24–30.
13 Jajoo M, Singh A, Arora N, Bhaskar V, Mandal A. Early total versus gradually advanced enteral nutrition in stable very-low-birth-weight preterm neonates: a randomized, controlled trial. *Indian J Pediatr* 2022; **89:** 25–30.
14 Alshaikh BN, Hassan O, Alburaki W, et al. Early exclusive enteral feeding in 30–33 weeks gestation infants: a randomized controlled trial. *J Perinatol* 2025; **45**: 628–34.
15 Razzaghy J, Shukla VV, Gunawan E, Reeves A, Nguyen K, Salas AA. Early and exclusive enteral nutrition in infants born very preterm. *Arch Dis Child Fetal Neonatal Ed* 2024; **109:** 378–83.
16 Mitchell E, Oddie SJ, Dorling J, et al. Implementing two-stage consent pathway in neonatal trials. *Arch Dis Child Fetal Neonatal Ed* 2021; **108:** 79–82.
17 Smith VC. Discharge planning considerations for the neonatal intensive care unit. *Arch Dis Child Fetal Neonatal Ed* 2021; **106:** 442–45.