ntrolled Trial of Two Incremental Milk Feeding Rates in Preterm Infants

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ABSTRACT

Background

Observational data have shown that slowly advancing enteral feeds in preterm infants is associated with reduced risk for necrotizing enterocolitis but increased risk for late onset sepsis. However, randomized trial data are limited.

Methods

We randomized very preterm or very low birthweight (VLBW) infants to daily milk increments of 30 or 18ml/kg/day until reaching full feeds. The primary outcome was survival without moderate or severe neurodevelopmental disability at 24 months. Secondary outcomes included components of the primary outcome, confirmed or suspected late onset sepsis, necrotizing enterocolitis and cerebral palsy.

Results

Among 2,804 infants randomized, the primary outcome was classifiable in 1224 (87.4%) of infants allocated to faster and 1246 (88.7%) to slower increments. Survival without moderate or severe neurodevelopmental disability at 24 months occurred in 802/1224 (65.5%) of infants allocated to faster and 848/1246 (68.1%) allocated to slower increments (adjusted risk ratio (RR), 0.96; 95% Confidence interval (CI), 0.92 to 1.01; p=0.16). Late onset sepsis occurred in 414/1389 (29.8%) of the faster and 434/1397 (31.1%) of the slower increment group (adjusted RR 0.96; 95% CI 0.86 to 1.07). Necrotizing enterocolitis occurred in 70/1394 (5.0%) of the faster and 78/1399 (5.6 %) of the slower group (adjusted RR 0.88; 95% CI, 0.68 to 1.16).

Conclusions

There was no significant difference in survival without moderate or severe neurodevelopmental disability at 24 months in very preterm or VLBW infants with a strategy of advancing milk feeds in daily increments of 30ml/kg versus 18ml/kg.

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INTRODUCTION

Very preterm (<32 weeks) and very low birthweight (<1500g, VLBW) infants are fed increasing volumes of milk per day until they reach full enteral feeds. The approach to increasing the feeding volume per day is uncertain because of competing concerns. Observational studies have shown higher risk of necrotizing enterocolitis.[1–3] with rapid advancement of feed volumes, but are subject to bias; one was an uncontrolled study before and after the introduction of a slowly progressive tube feeding schedule [1], and two were small case-control studies.[2,3] Slower advances in feed volume might, however, increase the risk of late onset sepsis from longer exposure to parenteral feeding as shown in a meta-analysis that also revealed no increase in necrotizing enterocolitis.[4] These conditions are both major causes of mortality and morbidity, including adverse neurodevelopmental outcome.[5–8]

Existing trial data are insufficient to determine whether advancing enteral feed volumes slowly (typically <24ml/kg/day) versus more quickly (daily increments of 30 to 40ml/kg) affects outcomes of very preterm or VLBW infants.[4,9–17] The Speed of Increasing milk Feeds Trial (SIFT) therefore compared faster (30ml/kg) versus slower (18ml/kg) daily increments in milk feeds.

METHODS

Trial design and procedures

The trial was a multicenter, parallel group, randomized controlled trial that followed a published protocol[18], also available at NEJM.org. The study was approved by the East Midlands National Research Ethics Committee and the National Maternity Hospital Ethics

Committee in Dublin and overseen by independent steering and data and safety monitoring committees.

Trial participants

Following written informed parental consent, infants receiving less than 30ml/kg/day of milk at randomization were eligible to participate if they were born before 32 weeks' gestation, and/or had a birthweight of less than 1500g. Infants with a known severe congenital anomaly, no realistic chance of survival, or who were unlikely to be traceable for follow-up, were ineligible.

Enrolment and treatment

When clinicians were ready to start advancing feed volumes, infants were allocated randomly to receive 30ml/kg or 18ml/kg daily increments in feed volume. Computerized randomization was performed through a secure website hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit, University of Oxford. A minimization algorithm balanced prognostic factors: hospital, multiple birth, gestational age range (Table 1), and birthweight <10th centile for gestational age. Multiple births were allocated to the same treatment. All other aspects of feeding and care followed routine clinical practice in the individual units, including the capacity to stop or alter the rate of increase in feeds if clinically indicated. Data were collected at study entry including whether the infant had absent or reversed end diastolic flow identified on any antenatal ultrasound scan.

Primary and secondary outcomes

The primary outcome was survival without moderate or severe neurodevelopmental disability at 24 months of age corrected for gestation. Moderate or severe

neurodevelopmental disability was defined as any of: moderate/severe visual impairment (reduced vision uncorrected with aids; or blind in one eye with good vision in the contralateral eye; or blind/perceives light only), or, moderate/severe hearing impairment (hearing loss corrected with aids; or some hearing loss but not corrected by aids; or deaf), or, moderate/severe gross motor impairment (unable to walk or sit independently), or, moderate/severe cognitive impairment assessed using the Parent Report of Children's Abilities-Revised (PARCA-R) or clinical data if missing. Total PARCA-R scores <44 (range 0 to 158, lower scores indicating greater  airment) were used to identify children with moderate/severe developmental impairment.[19]

Secondary outcomes included mortality, death before discharge home, microbiologically-confirmed or clinically suspected late onset sepsis from trial entry to discharge home, Bell's stage 2 or 3 necrotizing enterocolitis from trial entry to discharge home, time taken to reach full milk feeds (tolerating 150ml/kg/day for 3 consecutive days), growth (change in weight and head circumference z-score for gestational age) from birth to discharge home, duration of parenteral feeding, duration of time in intensive care, duration of hospital stay to discharge home, diagnosis of cerebral palsy by a doctor or other health professional, moderate or severe neurodevelopmental disability at 24 months corrected gestational age, plus the individual components of the definition of moderate or severe neurodevelopmental disability.

Classifications of moderate or severe neurodevelopmental disability, late onset sepsis and necrotizing enterocolitis were confirmed by blinded end-point review committee using standard definitions if outcomes were ambiguous or data missing (supplementary appendix). All data collection forms were assessed independently by pairs of clinicians

unaware of [illegible]cation. Owing to 'rounding' of the feed rate to the nearest 0.5ml, or small changes in a daily weight in the clinical setting, some infants on 'full feeds' only received 146-149ml/kg/day. We therefore considered a baby to be on full feeds if at least 145ml/kg/day was tolerated for 3 consecutive days. Cases not meeting these criteria were reviewed by the endpoint review committee to determine if a sustained level of feeding at a level below this had been achieved. Examples of this included feeds being stopped during transfer or a procedure, and higher calorie formula use.

Sample size and power

We estimated that 80% of infants would survive to 2 years, and 11% of survivors would have moderate or severe neurodevelopmental disability.[20] We anticipated the primary outcome would occur in 71% of the comparator (slower increment) group. With a total sample size of 2500, and allowing for a questionnaire response rate of 80%, there would be 90% power to detect an absolute difference [illegible]3 percentage points with a two-sided 5% significance level. Similarly, 2500 infants would have 90% power to detect an absolute difference of 5.4 percentage points (from 25.0% in the comparator group) in the incidence of late onset sepsis[21] and an absolute difference of 3.5 percentage points (from 6.0% in comparator group) in the incidence of necrotizing enterocolitis ([illegible]s stage 2 or 3).[22–24]

Subsequently, an inflation factor of 1.12 was applied to the sample size to allow for multiple births, since they received the same allocation and we anticipated correlated outcomes. This adjustment assumed the proportion of multiple births to be 25% and an intra-class correlation coefficient of 0.9 for the primary outcome at 24 months corrected for gestation.[25] The total target sample size was therefore increased to 2800.

Statistical analysis

Demographic factors, clinical characteristics and outcomes were summarized with counts and percentages for categorical variables, mean (SD) for normally distributed continuous variables, and median (interquartile or simple ranges) for other continuous variables. Outcomes were analyzed by intention to treat using the slower increment group as the comparator.

Risk ratios and 95% confidence intervals (CI) were calculated for the primary outcome at 24 months corrected for gestation and for the discharge outcomes of late onset sepsis and necrotizing enterocolitis. 99% CI were used for all other dichotomous outcomes, to take account of the number of hypothesis tests performed, without adjustment for multiple testing. For normally distributed continuous outcomes, the mean difference (99% CI) was presented, and the median difference (99% CI) for skewed continuous variables. Adjusted risk ratios (ARR) were estimated using log binomial regression, or log Poisson regression with a robust variance estimator if the binomial model failed to converge. Linear regression was used for normally distributed continuous variables and quantile regression for skewed continuous variables. The primary inference was based on the analysis adjusting for the minimization factors at randomization. Center was fitted as a random effect and the other minimization factors were fitted as fixed effects. Mother's identification was nested within center to take account of the additional level of clustering due to multiples and siblings. This adjusts the standard error to allow for the lack of independence in trial allocation and the potential correlation in outcome.

The consistency of the effects of advancing milk feeds on the incidence of the primary outcome, late onset sepsis and necrotizing enterocolitis across specific subgroups were assessed using the statistical test of interaction. Pre-specified subgroup analyses included:

(i) week of gestation at birth, (ii) birthweight <10th centile for gestational age versus ≥10th centile, and (iii) type of milk received during the hospital stay (breast milk only/formula only/mixed). Post-hoc analysis assessed the effect of the increments on late onset sepsis and necrotizing enterocolitis in babies with absent or reversed antenatal Doppler ultrasound flow velocity. Other deviations from the protocol include the use of quantile regression instead of Cox regression to analyse time to full feeds (as the Cox proportional hazard assumption was not satisfied), and mixed effect log binomial/Poisson models instead of generalized estimating equations(due to the ease and flexibility of these methods, which were not in common use when the study was conceived). We performed sensitivity analysis to examine the impact of missing data at 24 months on the primary outcome, by considering different scenarios departing from the assumption that data were missing completely at random.

RESULTS

Participants

2804 infants were recruited between 06/08/13 and 06/30/15 from 55 hospitals. Infant and maternal characteristics were similar in the two study groups (Tables 1, S3a-c). All infants received the allocated intervention, but 69 discontinued the intervention, 66 from clinician or parental preference and 3 from transfer to a non-participating hospital (Figure 1). For 11 infants, parental consent was withdrawn and their data were not available for analysis. The remainder were included in modified intention to treat analyses. Outcome data at discharge home were not available for 8 infants; their data were included in analyses except when knowledge of discharge or the date of discharge was required. 68 of the faster and 77 of the slower increment group died before 24 months corrected for gestational age (Table 2).

Primary outcome classification at 24 months corrected for gestation was possible in 1224 (87.4%) faster and 1246 (88.7%) slower increment infants (Figure 1).

Primary and secondary outcomes at 24 months of age corrected for prematurity

At 24 months corrected for gestation, death occurred in 68/1224 (5.6%) faster and 77/1246 (6.2%) of the slower increment group, and moderate or severe disability in 354 faster and 321 of the slower increment group (Table 2). There was no significant difference between infants receiving faster (30ml/kg) or slower (18ml/kg) daily increments in the primary outcome of survival without moderate or severe disability at 24 months corrected for gestation with faster versus with slower increments (Table 2). There were also no significant differences in the individual components of the composite outcome between the faster and slower increment groups. The results were comparable in sensitivity analyses of missing data using different approaches to impute missing data (Table S5b).

Secondary outcomes

The faster increment group reached full milk feeds at a median 7 days, versus 10 days in the slower increment group (adjusted median difference, -2.7 days; 99% CI, -3.1 to -2.4 days); the number of days of parenteral nutrition from trial entry was 9 and 11 days, respectively (adjusted median difference, -2.2 days; 99% CI, -2.7 to -1.6 days) (Table 3). There was no evidence of between-group differences for confirmed or clinically suspected late onset sepsis, Bell Stage 2 or 3 necrotizing enterocolitis, death during hospitalization, weight and head circumference standard deviation scores at discharge, duration of time in intensive care and duration of hospital stay from trial entry (Table 3).

After adjustment for minimization factors, moderate or severe motor impairment occurred in 7.5% of faster and 5.0% of slower increment groups (ARR, 1.48; 99% CI, 1.02 to 2.14) (Table 2). There was no suggestion of between group differences for the other 3 components of the disability definition.

Subgroup analyses

There was weak evidence of statistical interaction between the type of milk (breast only, mixed, formula only) and feeding increment with survival without moderate or severe disability to 24 months corrected for gestation (p=0.045). For infants fed with formula only, survival without moderate or severe disability was seen in 12/30 (40%) infants with faster increments compared to 28/40 (70%) infants with slower increments (Figures 2&S5c). There was no evidence of differential treatment effects for any other pre-specified subgroup from trial entry until discharge or at 24 months corrected for gestation (Figures 2, S2&S3). Post-hoc analysis did not show an interaction between antenatal absent or reversed end diastolic umbilical flow and faster or slower feed increments (Table S1&S2).

Serious Adverse Events

Four serious adverse events not pre-specified as outcomes were reported. One infant in each group developed an intra-cardiac thrombus, one extending into the superior vena cava causing renal failure and death (30ml/kg/day). One infant (30ml/kg/day) developed conjugated hyperbilirubinemia, which resolved, and one infant (18ml/kg/day) became dehydrated briefly with a central line extravasation.

DISCUSSION

In this large, pragmatic, randomized controlled trial involving infants below 32 weeks gestation or less than 1500 grams, advancing milk feeds at daily increments of 30 compared to 18ml/kg did not affect survival without moderate or severe disability at 24 months corrected for gestation. The speed of increment in feeds also did not affect the risks of late onset sepsis, necrotizing enterocolitis, or death during hospitalization.

Secondary outcome analysis suggested the number of days to reach full milk feeds and the number days of parenteral nutrition were lower with faster increments. Although these feeding outcomes seem  avor faster increments, there was an unexpected increase observed in the risk of moderate or severe motor impairment in the faster group that warrants consideration. This observation is unexplained and there were not more cases of late onset sepsis or necrotizing enterocolitis in the faster group. It is possible that it is a chance finding, as it was one of multiple secondary outcomes assessed, but biologically plausible explanations include increased cardiorespiratory events from pressure on the diaphragm or inability to absorb enteral nutrition.

The trial was pragmatic, and, apart from daily milk volume increments, clinician preference and unit guidelines determined other care. The primary outcome could be classified in 86.8% of the faster and 88.1% of the slower increment group at 24 months corrected for gestation. Comparable results were obtained from sensitivity analyses imputing missing data.

As compared with previous trials[9–17], the present trial included larger numbers of high-risk infants, including 1020 extremely low birthweight (ELBW) infants, 994 extremely preterm infants and 435 infants with umbilical artery absent or reversed end diastolic flow on antenatal Doppler studies. Subgroup analyses of higher risk infants were reassuring as

there was no suggestion of worse outcomes with faster increments. Infants were a median of 4 days old at commencement of the intervention and therefore the trial does not inform the relative safety of these feed advancement increments in the first few days after birth. Further study would be needed to address feeding in these infants, other speeds of advancing feeds or different milks.

Observational data have suggested a reduced risk of necrotizing enterocolitis in in very preterm or VLBW infants fed breast milk .[26] Most participating infants in SIFT were fed, at least partially, with breast milk. Only 3.3% of infants were fed formula milk alone, with similar numbers in the 2 groups. The finding of a poorer outcome in the relatively small number of faster increment, formula-only infants likely represents a chance finding given the small numbers, substantial loss to follow-up, and multiple comparisons performed without adjustment for multiple testing. The risk-benefit balance of enteral feeding strategies may differ between human milk-fed and formula-fed infants.

The trial was unblinded as it was considered impractical to completely blind caregivers and parents. This is unlikely to have influenced the ascertainment of the most important outcomes, which were reviewed by blinded endpoint review committees. Although it is possible that knowledge of allocation could alter clinician practice(for example, differentially stopping feeds given at faster versus slower increments in cases of suspected necrotizing enterocolitis), this is unlikely to have substantively affected results.

Infants born at extremely early gestational ages or with extremely low birthweight may react differently to the speed of increasing feeds. We did not find appreciable differences in outcome according to these variables, but our study included relatively small numbers of infants in these categories, and further research may be warranted in these groups.

In summary, the speed of advancing enteral feed volumes – daily increments of 18 versus 30 ml/kg -- did not have a significant impact on the primary outcome of survival without moderate or severe neurodevelopmental disability, nor affect the risks of late onset sepsis or necrotizing enterocolitis in very preterm or VLBW infants.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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FIGURE LEGENDS

Figure 1: Trial profile

Figure 2: Subgroup analyses for survival without moderate or severe disability to 24 months of age corrected for prematurity[a] Not adjusted for multiple comparisonsn and should not be used to infer definitive treatment effects.

Table 1: Infant and maternal characteristics at trial entry

	Faster Increment (30ml/kg/day) (n=1394)	**Slower Increment (18ml/kg/day) (n=1399)**
Male sex, n/N (%)	739 / 1394 (53.0)	726 / 1398 (51.9)
Infant median age at randomization (days) - (IQR)	4 (3 to 6)	4 (3 to 6)
Birthweight <10th centile for gestational age, n/N (%)	295 / 1394 (21.2)	291 / 1398 (20.8)
Gestation at delivery (completed weeks), n/N (%)		
Median (IQR)	29 (27 to 30)	29 (27 to 30)
23^{+0} to 25^{+6}	205 / 1394 (14.7)	201 / 1399 (14.4)
26^{+0} to 27^{+6}	291 / 1394 (20.9)	297 / 1399 (21.2)
28^{+0} to 29^{+6}	377 / 1394 (27.0)	383 / 1399 (27.4)
30^{+0} to 31^{+6}	432 / 1394 (31.0)	432 / 1399 (30.9)
32^{+0} to 36^{+6}	88 / 1394 (6.3)	86 / 1399 (6.1)
$\geq 37^{+0}$	1 / 1394 (0.1)	0 / 1399 (0.0)
Birthweight (grams), n/N (%)		
Mean (SD)	1144.2 (339.3)	1142.3 (328.9)

<500g	10 / 1394 (0.7)	7 / 1399 (0.5)
500 to 1000g	494 / 1394 (35.4)	509 / 1399 (36.4)
1000 to 1500g	661 / 1394 (47.4)	677 / 1399 (48.4)
≥1500g	229 / 1394 (16.4)	206 / 1399 (14.7)
Infant heart rate >100bpm at 5 mins, n/N (%)	1263 / 1374 (91.9)	1265 / 1381 (91.6)
Infant mean worst base excess within first 24 hours of birth (SD)	-6.1 (4.0)	-6.1 (3.9)
Infant ventilated via endotracheal tube at randomisation, n/N (%)	316 / 1392 (22.7)	293 / 1397 (21.0)
Infant had absent or reverse end diastolic flow, n/N (%)	209 / 1372 (15.2)	226 / 1380 (16.4)
Median time from trial entry to first feed (days) – (IQR)	0 (0 to 0)	0 (0 to 1)
Mother's mean age at randomization (years) – (SD)	30.5 (6.2)	30.7 (6.2)
Multiple pregnancy[a], n/N (%)	412 / 1394 (29.6)	411 / 1399 (29.4)
Singles[b]	3	5
Twins[c]	358	359
Triplets[d]	51	47
Caesarean section delivery, n/N (%)	841 / 1393 (60.4)	847 / 1399 (60.5)
Membranes ruptured >24h before delivery, n/N (%)	323 / 1377 (23.5)	338 / 1380 (24.5)

Unless otherwise stated the table gives the percentages of infants with data in that arm of the trial who had (or whose mother had) the stated characteristic.

[a]Sometimes, only one infant from a multiple pregnancy met the inclusion criteria and was recruited

[b]Number of infants from multiple pregnancies where the other fetuses were aborted, miscarried or stillborn

[c]Number of infants who were one of twins

[d]Number of infants who were one of triplets

Missing data (faster, slower); Male sex, 0, 1. Birthweight <10th centile for gestational age, 0, 1. Infant heart rate >100bpm at 5 mins, 20, 18. Infant worst base excess within first 24 hours of birth, 29, 26. Infant ventilated via endotracheal tube at randomisation, 2, 2. Infant had absent or reverse end diastolic flow, 22, 19. Time from trial entry to first feed (days), 5, 4. Mother's age at randomisation, 0, 1. Caesarean section delivery, 1, 0. Membranes ruptured >24h before delivery, 17, 19.

More detail on the gestational ages and birthweights and other outcomes are provided in the supplementary appendix Table S7.

Table 2: Primary and secondary outcomes at 24 months of age corrected for prematurity

Outcome at 24 months of age corrected for prematurity	Faster increment (30 ml/kg/day) (n = 1394)	Slower increment (18 ml/kg/day) (n = 1399)	Unadjusted effect measure (CI)[ab]	Adjusted effect measure (CI)[abc]
Primary outcome			*95% confidence intervals*	
Survival without moderate or severe disability[de], n/N (%)	802 / 1224 (65.5)	848 / 1246 (68.1)	0.96 (0.91, 1.02)	0.96 (0.92, 1.01)
Survival, n/N (%)	1326 / 1394 (95.1)	1322 / 1399 (94.5)	1.01 (0.99, 1.02)	1.01 (0.99, 1.03)
Moderate or severe disability, n/N (%)	354 / 1156 (30.6)	321 / 1169 (27.5)	1.12 (0.98, 1.28)	1.10 (0.97, 1.25)
Secondary outcome			*99% confidence intervals*	
Moderate or severe visual impairment, n/N (%)	21 / 1156 (1.8)	16 / 1171 (1.4)	1.33 (0.57, 3.10)	1.28 (0.43, 3.83)
Moderate or severe hearing impairment, n/N (%)	58 / 1143 (5.1)	41 / 1172 (3.5)	1.45 (0.86, 2.46)	1.43 (0.79, 2.57)
Moderate or severe motor impairment, n/N (%)	87 / 1164 (7.5)	59 / 1177 (5.0)	1.49 (0.96, 2.32)	1.48 (1.02, 2.14)
Moderate or severe cognitive impairment, n/N (%)	307 / 1156 (26.6)	289 / 1170 (24.7)	1.08 (0.89, 1.30)	1.06 (0.89, 1.27)
Parent Report of Children's Abilities - Revised (PARCA-R)			*99% confidence intervals*	
Composite score				
Mean (SD)	72.5 (38.3)	73.9 (37.8)	-1.46 (-6.31, 3.39)	-0.62 (-4.82, 3.59)
Non-verbal Cognition Scale:				
Mean (SD)	25.1 (6.2)	25.5 (5.7)	-0.45 (-1.18, 0.29)	-0.36 (-1.01, 0.29)
Vocabulary Sub-scale:				
Mean (SD)	39.3 (29.7)	40.3 (30.1)	-0.99 (-4.81, 2.83)	-0.37 (-3.71, 2.97)

Sentence Complexity Sub-scale:				
Mean (SD)	7.9 (5.7)	7.9 (5.4)	-0.09 (-0.79, 0.61)	-0.05 (-0.73, 0.64)
Diagnosis of cerebral palsy by a doctor or other health professional, n/N (%)	58 / 1084 (5.4)	35 / 1099 (3.2)	1.68 (0.97, 2.91)	1.66 (0.97, 2.84)

[a]Risk ratios for binary outcomes and mean differences for continuous outcomes.

[b]95% confidence intervals for survival without moderate/severe disability, survival, and moderate/severe disability at 24 months corrected for gestational age. 99% confidence intervals for all other outcomes, but these have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

[c]As per prespecified plan, adjusted for minimization factors; collaborating hospital, single or multiple birth, gestational age at birth, and birthweight less than the 10th centile for gestational age where technically possible..

[d]p-value for testing whether adjusted risk ratio is equal to 1, p=0.16.

[e]Moderate/Severe disability is defined as one or more of the following: visual impairment, hearing impairment, motor impairment or cognitive impairment (PARCA-R Composite Score <44). Definitions of motor and sensory impairments are defined in the report published by British Association of Perinatal Medicine (BAPM) in 2008.

Missing data (faster, slower); Survival without moderate or severe disability, 170,153. Survival, 0,0. Moderate or severe disability, 238,230. Moderate or severe visual impairment, 238, 228. Moderate or severe hearing impairment, 251, 227. Moderate or severe motor impairment, 230, 222. Moderate or severe cognitive impairment, 238, 229. Parent Report of Children's Abilities - Revised (PARCA-R); Composite score, 419, 392; Non-verbal Cognition Scale; 414, 390; Vocabulary Sub-scale, 412, 383; Sentence Complexity Sub-scale: 405,379. Diagnosis of cerebral palsy by a doctor or other health professional, 310, 300.

Table 3: Outcomes at discharge to home

Outcome from trial entry until discharge home	Faster increments (30ml/kg/day) (n = 1394)	Slower increments (18ml/kg/day) (n = 1399)	Unadjusted effect measure (CI)[ab]	Adjusted effect measure (CI)[abc]
Primary discharge outcome			*95% confidence intervals*	
Microbiologically-confirmed or clinically suspected late onset sepsis, n/N (%)	414 / 1389 (29.8)	434 / 1397 (31.1)	0.96 (0.85, 1.08)	0.96 (0.86, 1.07)
necrotizing enterocolitis (Bell stage 2 or 3), n/N (%)	70 / 1394 (5.0)	78 / 1399 (5.6)	0.90 (0.66, 1.24)	0.88 (0.68, 1.16)
Secondary outcome			*99% confidence intervals*	
Death before discharge, n/N (%)	60 / 1392 (4.3)	65 / 1393 (4.7)	0.92 (0.59, 1.45)	0.91 (0.55, 1.53)
Time taken to reach full milk feeds (145 ml/kg/day for 3 consecutive days)				
Median {IQR] and median difference	7 {7, 10}	10 {9, 13}	-3.0 (-3.3 to -2.7)	-2.7 (-3.1 to -2.4)
Weight Standard Deviation Score at discharge home[d]				
Mean [SD] and mean difference	-1.5 [1.1]	-1.5 [1.1]	-0.04 (-0.15 to 0.08)	-0.02 (-0.11 to 0.08
Head circumference Standard Deviation Score at discharge home[d]				
Mean [SD] and mean difference	-0.8 [1.5]	-0.7 [1.7]	-0.09 (-0.27 to 0.09)	-0.07 (-0.24 to 0.10
Duration of parenteral feeding from trial entry to discharge home:				
Median {IQR} and median difference	9 {7, 14}	11 {9, 16}	-2.0 (-2.4 to -1.6)	-2.2 (-2.7 to -1.6)
Length of time in intensive care from trial entry to discharge home:				
Median {IQR} and median difference	7 {4, 21}	8 {4, 21}	-1.0 (-2.6 to 0.6)	-0.4 (-1.5 to 0.6)

Length of hospital stay from trial entry to discharge home[e]				
Median {IQR} and median difference	54 {37, 81}	55 {38, 78}	-1.0 (-5.2 to 3.2)	0.1 (-1.9 to 2.0

[a]Risk ratios for binary outcomes.

[b]95% confidence intervals for late onset sepsis and necrotizing enterocolitis (Bell stage 2 or 3). 99% confidence intervals for all other outcomes, but these have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects.

[c]As per prespecified plan, adjusted for minimization factors; collaborating hospital, single or multiple birth, gestational age at birth, and birthweight <10th centile for gestational age where technically possible.

[d] Calculated using The British 1990 growth reference (revised September 2009). The standard deviation scores (SDS) indicate how far a baby is from the population mean weight and head circumference for babies of the same age and sex. So, for example, babies with a SDS of -2 or below compare approximately with the bottom 2% of the reference population.

[e]Surviving infants only

Missing data (faster, slower); Microbiologically-confirmed or clinically suspected late onset sepsis, 5,2. Necrotizing enterocolitis (Bell stage 2 or 3), 0,0. Death before discharge, 2,6. Time taken to reach full milk feeds (145 ml/kg/day for 3 consecutive days), 72,102. Weight Standard Deviation Score at discharge home, 75,77. Head circumference Standard Deviation score at discharge home, 258,228. Duration of parenteral feeding from trial entry to discharge home, 10,21. Length of time in intensive care from trial entry to discharge home, 71,87. Length of hospital stay from trial entry to discharge home, 62,71.