# Two speeds of increasing milk feeds for very preterm or very low-birthweight infants: the SIFT RCT

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# Scientific summary

## The SIFT RCT

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# Scientific summary

## Background

Very preterm (< 32 weeks) or very low-birthweight (< 1500 g) infants are fed increasing volumes of milk per day, until they reach full enteral feeds. The safest approach is uncertain, with competing concerns that advancing feed volumes quickly might increase the risk of necrotising enterocolitis but that slower advances in feed volume might increase the risk of late-onset sepsis from longer exposure to parenteral fluids. As these outcomes and other factors can influence neurodevelopmental outcomes, feeding interventions (including speed of milk increments) might alter the long-term outlook of very preterm or very low-birthweight infants.

Existing trial data are insufficient to determine whether advancing enteral feed volumes slowly (typically < 24 ml/kg/day) or more quickly (30–40 ml/kg/day) affect these outcomes in very preterm or very low-birthweight infants. None of the nine randomised controlled trials included in the Cochrane review prior to the Speed of Increasing milk Feeds Trial (SIFT) published neurodevelopmental outcomes (Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low-birthweight infants. *Cochrane Database Syst Rev* 2015;**10**:CD001241). The review authors concluded 'that advancing enteral feed volumes at daily increments of 30 to 40 ml/kg (compared to 15 to 24 ml/kg) does not increase the risk of necrotising enterocolitis or death in very low-birthweight infants'. They also concluded that 'advancing the volume of enteral feeds at slow rates results in several days of delay in establishing full enteral feeds and increases the risk of invasive infection'. 'The applicability of these findings to extremely preterm, extremely low-birthweight, or growth-restricted infants is limited' owing to the participants studied and 'further randomised controlled trials in these populations may be warranted to resolve this uncertainty' (Morgan J, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low-birthweight infants. *Cochrane Database Syst Rev* 2015;**10**:CD001241). The SIFT, therefore, compared faster (30 ml/kg/day) with slower (18 ml/kg/day) daily increments in milk feeds.

## Objectives

To study the effect of two different speeds of daily milk feed increments (30 ml/kg/day vs. 18 ml/kg/day) on survival without moderate or severe impairment at 24 months of age (corrected for gestational age), necrotising enterocolitis, late-onset sepsis and other morbidities in very preterm or very low-birthweight infants. We also assessed the economic impact of the two daily feed increments, interviewed parents about taking part in multiple studies and tested methods for improving questionnaire returns.

## Methods

### *Study design*

The study was a multicentre, two-arm, parallel-group, randomised controlled trial in very preterm or very low-birthweight infants (www.npeu.ox.ac.uk/sift; accessed 9 December 2019).

### *Setting*

The setting was UK and Republic of Ireland neonatal units; recruitment and initial care was in 55 units and continuing care during birth hospitalisation was in a further 78 units.

### *Participants*

The participants were infants born at < 32 weeks' gestation or who had a birthweight of < 1500 g, who were receiving < 30 ml/kg/day of milk. Infants with a known severe congenital anomaly, with no realistic chance of survival or who were unlikely to be traceable for follow-up, were ineligible. Written, parental consent was obtained from parents after a verbal and written explanation.

### *Interventions*

When clinicians were ready to start advancing feed volumes, the infant was allocated randomly via secure web-based randomisation to receive daily increments in feed volume of 30 ml/kg or 18 ml/kg. A minimisation algorithm was used to balance prognostic factors. Multiple births were given the same allocation. All other aspects of feeding and care followed routine clinical practice in the individual units.

## Outcomes

### *Primary outcome*

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

### *Secondary outcomes*

The secondary outcomes were:

- mortality
- moderate or severe neurodevelopmental disability at 24 months corrected for gestational age
- microbiologically confirmed or clinically suspected late-onset invasive sepsis
- necrotising enterocolitis (Bell's stage 2 or 3)
- time taken to reach full milk feeds (150 ml/kg/day for 3 consecutive days)
- growth
- duration of parenteral feeding
- time in intensive care
- duration of hospital stay
- diagnosis of cerebral palsy by a doctor or other health professional
- individual components of the definition of moderate or severe neurodevelopmental disability.

Diagnoses of moderate or severe neurodevelopmental disability, late-onset sepsis and necrotising enterocolitis were confirmed by the blinded end-point review committee using standard definitions. All data collection forms were assessed independently by pairs of clinicians unaware of infant allocation.

## Statistics and analysis plan

### *Sample size*

It was estimated that 80% of infants would survive to 24 months of age and 11% of survivors would have moderate or severe neurodevelopmental disability. Estimating that the primary outcome would be seen in 71% of the comparator (slower) group, a total sample size of 2500 infants, allowing for a questionnaire response rate of 80%, would give 90% power to detect an absolute difference of 6.3% with a two-sided 5% significance level.

Subsequently, an inflation factor of 1.12 was applied to the sample size to allow for multiple births, as they received the same allocation and would probably have correlated outcomes. This adjustment assumed the proportion of multiple births to be 25% and an intraclass correlation coefficient of 0.9 for the primary outcome at 24 months corrected for gestational age. The total target sample size was therefore increased to 2800 infants.

### *Statistical analyses*

Demographic factors, clinical characteristics and outcomes were summarised with counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables and medians (interquartile or simple ranges) for other continuous variables. Outcomes were analysed according to allocation, using the slower feed increment group as the comparator.

Risk ratios and 95% confidence intervals were calculated for the primary outcome at 24 months corrected for gestational age and for the discharge outcomes of late-onset sepsis and necrotising enterocolitis, with 99% confidence intervals used for all other dichotomous outcomes. For normally distributed continuous outcomes, the mean difference (99% confidence interval) was presented and for skewed continuous variables the median difference (99% confidence interval) was presented. Adjusted risk ratios 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 was used for skewed continuous variables. The primary inference was based on the analysis adjusting for the minimisation factors at randomisation. Centre was fitted as a random effect and all other factors were fitted as fixed effects. The correlation in outcomes between multiples and siblings born in a subsequent pregnancy during the trial period was accounted for.

The consistency of the effects of advancing milk feeds on the incidence of the primary outcome, late-onset sepsis and necrotising enterocolitis across specific subgroups of infants was assessed using the statistical test of interaction. Prespecified subgroup analyses included (1) week of gestation at birth, (2) birthweight $<$ 10th centile versus $\geq$ 10th centile for gestational age and (3) type of milk received during the hospital stay. A non-prespecified analysis assessed the effect of the increments on sepsis and necrotising enterocolitis in infants with the presence of absent or reversed umbilical arterial blood flow on any antenatal umbilical Doppler study.

## Results

From June 2013 to June 2015, 55 hospitals recruited 2804 infants; 1400 infants were allocated to faster daily feed increments (30 ml/kg/day) and 1404 infants were allocated to slower feed increments (18 ml/kg/day). A total of 69 infants discontinued the intervention owing to clinician or parental preference; for 11 of these infants, parental consent was withdrawn and their data were not available for analysis and the remainder were included in the intention-to-treat analysis. Outcome data for discharge home were not available for eight infants; their data were included in analyses except when knowledge of discharge or the date of discharge was required. A total of 68 (4.9%) infants in the faster increment group and 77 (5.5%) in the slower increment group died before 24 months corrected for gestational age. Outcome data were available for 1175 (84.3%) of the surviving infants in the faster increment group and 1189 (85.0%) in the slower increment group at 24 months corrected for gestational age. Baseline characteristics were well balanced, with the median gestational age at birth being 29 weeks in both groups. Median birthweights were 1144 g in the faster increment group and 1142 g in the slower increment group. Overall, 60% of infants were born via caesarean section, 24% infants were born following rupture of maternal amniotic membranes for $>$ 24 hours and 16% of infants had evidence of absent or reversed end diastolic flow in the umbilical arteries.

### *Primary outcome*

The primary outcome (mortality or disability) was known for 1224 (87.2%) infants in the faster increment group and 1246 (89.0%) infants in the slower increment group. In the faster increment group, 802 out of 1224 (65.5%) infants survived to 24 months corrected for gestational age without moderate or severe disability, compared with 848 out of 1246 (68.1%) infants in the slower increment group: adjusted risk ratio 0.96 (95% confidence interval 0.92 to 1.01). There were no significant differences at 24 months corrected for gestational age in either component of the combined outcome (i.e. survival or moderate or severe disability).

### *Secondary outcomes at 24 months of age corrected for gestational age*

At 24 months corrected for gestational age, there was a significant difference between groups after adjustment for the factors used in the minimisation algorithm; moderate or severe motor impairment occurred in 87 out of 1164 (7.5%) infants in the faster increment group and 59 out of 1177 (5.0%) infants in the slower increment group (adjusted risk ratio 1.48, 99% confidence interval 1.02 to 2.14; $p = 0.007$).

There was, however, no evidence of a significant difference between groups on the other three components of the disability definition (moderate or severe visual, hearing or cognitive impairment). Numerically, more adverse outcomes were seen in the faster increment group for each of these components and for the diagnosis of cerebral palsy by a doctor or other health professional, which occurred in 5.4% of the faster increment group and 3.2% of the slower increment group (adjusted risk ratio 1.66, 99% confidence interval 0.97 to 2.84; $p = 0.015$).

### *Other secondary outcomes*

In total, 414 of 1389 (29.8%) infants in the faster increment group had microbiologically confirmed or clinically suspected late-onset sepsis compared with 434 of 1397 (31.1%) infants in the slower increment group (adjusted risk ratio 0.96, 95% confidence interval 0.86 to 1.07; $p = 0.43$). Bell's stage 2 or 3 necrotising enterocolitis occurred in 70 out of 1394 (5.0%) infants in the faster increment group and 78 out of 1399 (5.6%) infants in the slower increment group (adjusted risk ratio 0.88, 95% confidence interval 0.68 to 1.16; $p = 0.37$).

The faster increment group reached full milk feeds significantly sooner, with an adjusted median difference of −2.7 days (99% confidence interval −3.1 to −2.4 days; $p < 0.001$). Significantly fewer days of parenteral nutrition from trial entry were received in the faster increment group (adjusted median difference −2.2 days, 99% confidence interval −2.7 to −1.6 days; $p < 0.001$).

There was no evidence of between-group differences for other outcomes during hospitalisation.

### *Subgroup analyses*

Subgroup analyses showed a significant interaction ($p = 0.045$) with the primary outcome for the type of enteral milk received (human, formula or both). No significant interaction was seen with the primary outcome for completed weeks of gestation at birth or birthweight < 10th centile or ≥ 10th centile for gestational age ($p = 0.076$ and $p = 0.18$, respectively).

Subgroup analyses did not show any significant interactions with necrotising enterocolitis for:

- completed weeks of gestation at birth ($p = 0.63$)
- birthweight < 10th centile or ≥ 10th centile for gestational age ($p = 0.25$)
- type of enteral milk received (human, formula or both) ($p = 0.53$).

Subgroup analyses did not show any significant interactions with late-onset sepsis for:

- completed weeks of gestation at birth ($p = 0.07$)
- birthweight < 10th centile or ≥ 10th centile for gestational age ($p = 0.51$)
- type of enteral milk received (human, formula or both) ($p = 0.56$).

### *Other analyses*

Cost–consequence analysis showed that the faster feed increment rate was less costly than but also less effective than the slower rate in terms of achieving the primary outcome. It was therefore found to not be cost-effective. Interviews with parents showed that they valued opportunities for their infant to take part in studies, but this interaction is complex and difficult to remember at a stressful and

confusing time and made worse by considering multiple studies. More questionnaires were returned when vouchers were given before rather than after receiving them.

## Safety and adverse events

Four unexpected serious adverse events were reported, two in each group. No events were assessed as being causally related to the intervention.

## Discussion

Results from this large, pragmatic, randomised controlled trial show that advancing milk feeds at daily increments of 30 ml/kg compared with 18 ml/kg does not affect survival without moderate or severe disability at 24 months corrected for gestational age, or the risk of late-onset sepsis, necrotising enterocolitis, or death during hospitalisation in very preterm or very low-birthweight infants. The number of days to reach full milk feeds and days of parenteral nutrition were reduced with faster increments. Although these feeding outcomes favour faster increments, there was an unexpected increase in the risk of moderate or severe motor impairment in the faster increment group that must be considered. This observation is unexplained and there were not more cases of late-onset sepsis or necrotising enterocolitis in the faster increment group.

These results substantially outweigh data from previous trials because large numbers of high-risk infants were recruited, including 1020 extremely low-birthweight infants, 994 extremely preterm infants and 435 infants with absent or reversed end diastolic flow in the umbilical artery on antenatal Doppler studies. In the subgroup analyses, there was only evidence of excess adverse outcome in the small number of faster increment infants who received formula milk alone. Given the small numbers and the missing data, in the formula-only fed infants this probably represents a chance finding.

Higher-risk infants (including those with abnormal Doppler results) did not do worse with faster increments. Infants were a median of 4 days old at commencement of the intervention and some clinicians may have been less likely to enrol the highest-risk infants. The trial does not, therefore, allow conclusion about the safety of different feed advancement increments in the first few days after birth.

The high follow-up rates in survivors at 24 months corrected for gestational age of 87.4% of surviving infants in the faster increment group and 88.4% of surviving infants in the slower increment group suggest that the results are robust and unlikely to be biased and confirm the utility of parent-report questionnaires in combination with clinical data to obtain trial outcome measures.

### *Applicability*

The trial was pragmatic and, apart from the daily milk volume increment, clinician preference and unit guidelines determined other care. The SIFT, therefore, assessed the intention to increase at 18 ml/kg/day or 30 ml/kg/day by intention-to-treat analysis and recruited a mixed population including high-risk infants.

### *Limitations*

The trial was not blinded, as it would be difficult to safely and completely blind caregivers and parents to the feed rate. It is possible that knowledge of allocation could alter clinician practice, for example stopping feeds more often or diagnosing suspected necrotising enterocolitis in faster increment infants. We did, however, see fewer cases of necrotising enterocolitis in the faster increment group, suggesting that this did not occur often.

### *Implications for research*

Infants at the extremes of gestation or birthweight may react differently and further research may be warranted in these groups. Alternative increments of milk increases may also merit further examination, as might different increments with different milk types.

## Conclusions

Advancing enteral feed volumes at daily increments of 18 ml/kg versus 30 ml/kg did not affect the primary outcome of survival without moderate or severe neurodevelopmental disability, late-onset sepsis or necrotising enterocolitis in very preterm or very low-birthweight infants. Advancing feeds more quickly reduced the duration of parenteral nutrition by 2 days but was associated with an unexpected increase in the frequency of abnormal motor outcomes.

## Trial registration

This trial is registered as ISRCTN76463425.

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