Speed of increasing milk feeds

Protocol

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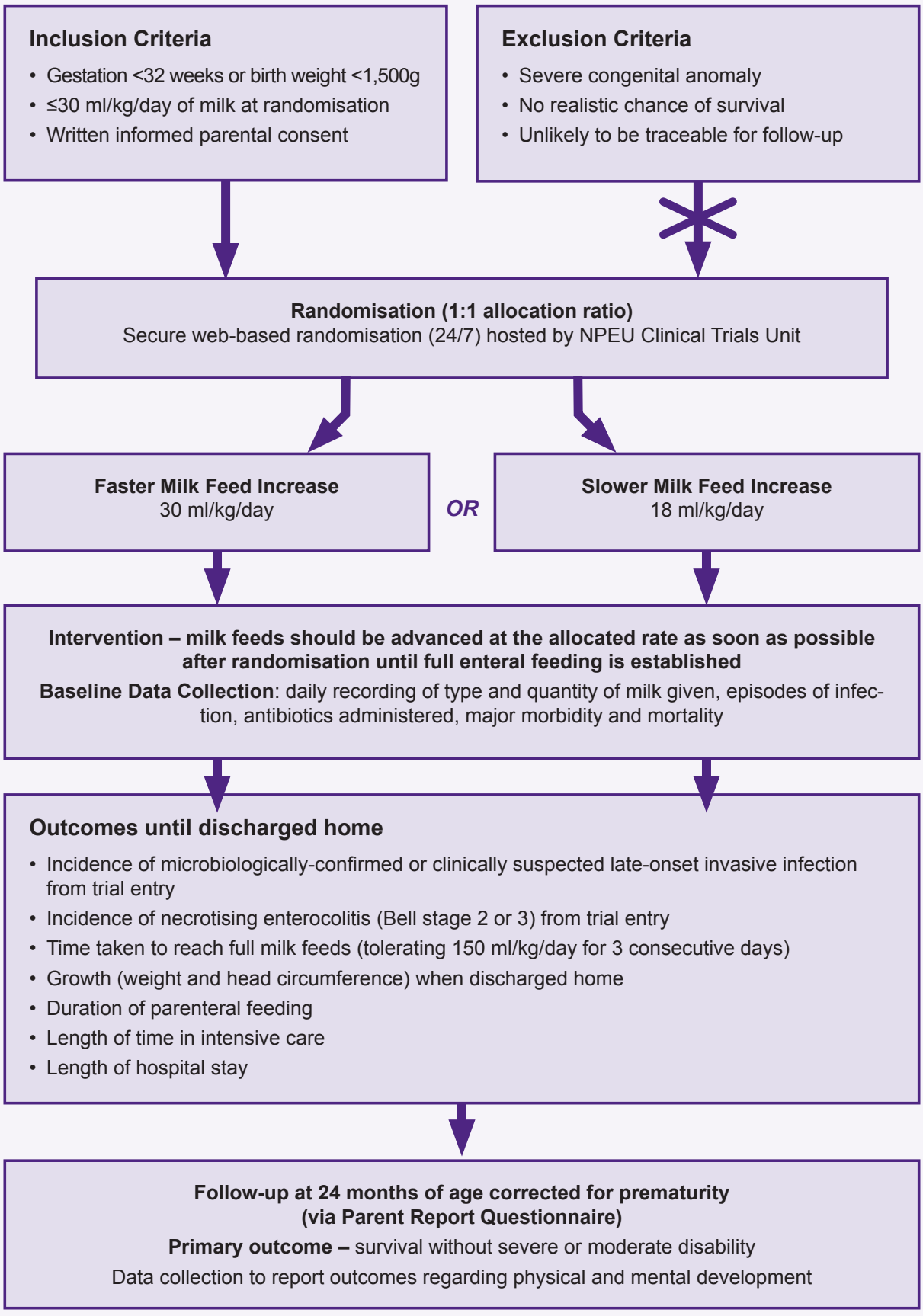
Trial Flow Diagram: Speed of Increasing milk Feeds Trial for very preterm or VLBW infants



Contents

1. Trial Summary

Study Title	SIFT – Speed of Increasing milk Feeds Trial
Internal ref. no.	SIFT01
Clinical Phase	Phase III
Trial Design	Multi-centre, randomised controlled trial
Trial Participants	Infants who are either (i) very preterm (<32 weeks) or (ii) very low birth weight (VLBW) [<1,500 g]
Inclusion Criteria	• Gestational age at birth <32 weeks, or birth weight <1,500 g • The infant is receiving ≤30 ml/kg/day of milk at randomisation • Written informed parental consent is obtained To ensure the widest applicability to preterm infants across the UK, those exclusively breast milk fed, formula milk fed, or receiving mixed feeds will be included
Exclusion Criteria	• Infants with a severe congenital anomaly • Infants who, in the opinion of the treating clinician, have no realistic chance of survival • Infants who are unlikely to be traceable for follow-up at 24 months of age corrected for prematurity (for example, infants of non-UK residents)
Planned Sample Size	2,800
Follow-up Duration	Participants will be followed up at 24 months of age corrected for prematurity via a parent report questionnaire
Planned Trial Period	72 months
Primary Objective	To assess and compare the effects of a faster (30 ml/kg/day) and a slower (18 ml/kg/day) increase in milk feed volumes on survival of very preterm (<32 weeks) or VLBW (<1,500 g) infants without moderate or severe disability at 24 months of age corrected for prematurity
Secondary Objectives	To assess and compare the effects of a faster (30 ml/kg/day) and a slower (18 ml/kg/day) increase in milk feed volumes on survival of very preterm (<32 weeks) or VLBW (<1,500 g) infants with respect to: • Incidence of microbiologically-confirmed or clinically suspected late-onset invasive infection from trial entry until discharged home • Incidence of necrotising enterocolitis (NEC) [Bell stage 2 or 3] from trial entry until discharged home • Time taken to reach full milk feeds (tolerating 150 ml/kg/day for 3 consecutive days) • Growth (weight and head circumference) when discharged home • Duration of parenteral feeding before discharged home • Length of time in intensive care • Length of hospital stay

2. Abbreviations

AE	Adverse Event
BAPM	British Association of Perinatal Medicine
CI	Chief Investigator
CSF	Cerebro-spinal Fluid
DCF	Data Collection Form
DMC	Data Monitoring Committee
HTA	Health Technology Assessment
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
LRN	Local Research Nurse
MCRN	Medicines for Children Research Network
NEC	Necrotising Enterocolitis
NHS	National Health Service
NIHR	National Institute for Health Research
NPEU CTU	National Perinatal Epidemiology Unit Clinical Trials Unit
NRES	National Research Ethics Service
PARCA-R	Parent Report of Children's Abilities - Revised
PI	Principal Investigator
PIL	Participant/Patient Information Leaflet
PMG	Project Management Group
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SIFT	Speed of Increasing milk Feeds Trial
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
VLBW	Very Low Birth Weight (defined as birth weight <1,500 g)

3. Introduction

3.1 Summary of Trial Design

This will be a multi-centre randomised controlled trial (RCT) to assess whether the speed of increasing milk feed volumes (faster increase [30 ml/kg/day] versus slower increase [18 ml/kg/day]) in very preterm (<32 weeks) or VLBW (<1,500 g) infants has any effect on survival without moderate or severe disability at 24 months of age corrected for prematurity.

The trial will recruit 2,800 infants from approximately 30 neonatal units within the UK and Ireland over 3 years.

3.2 Outcomes Affected by Feeding Strategies

In the UK, 1–2 % of newborn infants are very preterm (<32 weeks) or have very low birth weight (<1,500 g). Preterm birth is the major risk factor for infant mortality, with 73% of neonatal deaths in the United Kingdom occurring in infants born before 37 completed weeks of gestation[1]. As survival, especially of very preterm infants has increased in recent years[2], the high prevalence of morbidity associated with preterm birth means that the assessment of long-term outcomes has become increasingly important[3].

Short and long-term outcomes for preterm infants are affected by strategies that reduce infection rates, reduce NEC rates, promote adequate growth, and maintain access to tertiary level facilities. Optimising feeding strategies affects all of these outcomes. Benefits are therefore likely to arise both from the individual and combined effects of identifying the optimum feeding strategy, as the rates of such complications in preterm infants are high: NEC severe enough to cause death or require surgery affects approximately 7.5% of infants born before 29 weeks' gestation, and is the cause of death in 11% of the deaths of infants born before 32 weeks[4]. Late-onset infection affects around 25% of very preterm infants and is responsible for 10% of deaths in the same cohort. Long-term data following late-onset infection or NEC suggest these conditions almost double the risk of poor neurodevelopmental outcome[5].

Recent data also show that neonatal intensive care capacity in the UK is under extreme pressure, with infants regularly transferred due to lack of beds[6]. Published national data demonstrate the uncertainties and variation in feeding strategy in the UK[7,8]. Worryingly, only 28% of infants in a recent confidential National Health Service (NHS) survey (National Confidential Enquiry into Patient Outcome and Death – NCEPOD[9,10]) received appropriate intravenous nutrition management.

There is wide acceptance that randomised controlled trial data are urgently needed[11] and optimising feeding strategies in preterm infants was identified as a priority area at an MCRN prioritisation of neonatal research meeting in 2010.

A recently reported trial (ADEPT) performed across the UK indicated that starting milk feeds before 48 hours of age in the most at-risk group is beneficial, particularly for establishing earlier full milk feeds[12,13]. However, it did not examine infants who have grown normally in the womb (who are much more common), nor the rate of progression of milk feeds once started, nor examine outcomes after discharge. The proposed trial will include all infants born <32 weeks or <1,500 g regardless of the milk feed type (breast milk is preferred but many receive formula), which will broaden the clinical applicability of results.

3.3 Potential Benefits

Achieving full milk feeds sooner requires a shorter duration of intravenous nutrition and fewer indwelling intravenous lines and is associated with less sepsis and fewer liver problems. Preterm infants are also at significant risk of poor long-term neurodevelopmental problems with almost 12% having moderate or severe disability[14], with both sepsis and NEC dramatically increasing this risk[15,16].

Additionally, achieving full milk feeding sooner is associated with significant cost savings through decreased use of intravenous nutrition, a reduction in time spent in a specialist tertiary neonatal unit, shortened total hospital stay (potentially saving £1,000 per day), and reductions in societal costs due

to improved long-term outcomes[15–20]. Vacating tertiary level neonatal cots sooner will also improve the family's experience and the infant's safety by decreasing the need for transfer to other hospitals for intensive care.

Results of the recent EPICure 2 study comparing extremely preterm infants born in 2006 with 1995 indicate that although survival has improved, approximately one third of survivors are still affected by moderate or severe disability at 2.5 to 3 years of age[21]. Infection and NEC both remained highly predictive factors for long-term disability. Any reduction in either problem may therefore be expected to reduce long-term disability in this population. For these reasons, neurodevelopmental outcome at 2 years of age will be assessed and these data will be used to identify whether longer term follow-up at school age is needed for which additional funding would be sought.

Overall lifetime financial costs of disability are significant, and so preventing even a few cases and reducing cognitive problems at the population level would reduce the financial burden of long-term care for the NHS and society. No additional resources will be needed to implement the optimal feeding strategy which, if successful, could be adopted rapidly across the NHS at low cost.

3.4 Nutritional Support of Preterm Infants and Speed of Increasing Milk Feeds

Every year in the UK around 8,000 infants are born so preterm that they cannot initially be fed milk and require intravenous nutrition. Milk feeding is gradually increased as the immature gut begins to tolerate milk and intravenous nutrition is correspondingly reduced, but there are few data determining how quickly this is best achieved[11].

One of the most serious complications of intravenous feeding is late-onset sepsis, which occurs in 27% of infants born weighing less than 1,500 g at birth or under 29 weeks' gestation[11]. Late-onset sepsis is known to cause poor long-term cognitive outcomes, liver damage and sudden death from cardiac problems resulting from misplaced catheters[22–24]. One of the most common late-onset infections is 'catheter-related bloodstream infection'; the risk of bloodstream infection is directly related to the time the catheter is indwelling in the blood stream[25–27]. This is commonly assessed by the metric 'infections per 1,000 catheter days' and rates of between 5 and 15 infections per 1,000 catheter days are frequently reported. There is geographical and temporal clustering and inter-unit variation that are not fully explained by differences in case-mix[28,29]. Infection-control and catheter-management bundles have successfully reduced the rates but have not entirely eliminated infection[30–32]. In order to further reduce rates, there is a need to identify methods to reduce exposure to parenteral nutrition.

The more rapid advancement of enteral feeds described in this protocol will, in principle, cause infants to reach full milk feeds (tolerating 150 ml/kg/day for 3 consecutive days) about 4 days earlier than the slower advancement. This will reduce exposure to parenteral nutrition and catheters by approximately 4 days per infant, that is, 1,000 catheter days in 250 infants. Reducing exposure by this amount could reduce the number of infections by between 5 and 15 cases per 250 infants, which is an absolute risk reduction of 4%. This is possibly an underestimate of the reduction as infection risk increases with the length of time a catheter is in place[33,34].

However, faster increases in milk feed volumes may increase the likelihood of NEC which as well as being potentially fatal, may provoke gut intolerance which could result in longer times to achieving full feeds rather than shorter. Survivors of NEC also have significantly worse long-term outcomes across multiple domains than those unaffected.[21,22]

It can be seen therefore, that while emerging data suggest better health outcomes may be achieved with faster feeding increments, there are possible disadvantages and a randomised controlled trial is required to support a change in current clinical practice[11].

3.5 Currently Published Trial Evidence on the Speed of Milk Feed Increase

The Cochrane review of studies examining speeds of milk feed increase was updated in March 2011[11]. It included 496 infants from four trials and no further studies have been published since the review. All four trials showed a reduction in time to full milk feeds of between 2 and 5 days (median difference in the faster increase groups), clearly demonstrating that this intervention can feasibly impact late-onset sepsis. However, none reported the effect on infection or long-term outcomes nor were they powered

to assess effects on rates of NEC. The trial will use survival without moderate or severe disability at 24 months of age corrected for prematurity as the primary outcome and will also evaluate the resultant effect on sepsis, NEC, growth, and resource utilisation. These factors are strongly associated with brain damage, poor brain growth, and poor long-term outcomes[15].

3.6 Active or Proposed Trials on the Speed of Milk Feed Increase

Extensive searches have found no active or proposed studies investigating the rate of increasing milk feeds. There is one relevant Italian trial recruiting 120 infants: ACTRN12611000419965, Early Versus Late Progression of Enteral Feeding in VLBW Infants. This trial is examining the timing of when to start increasing milk feeds but not how fast they should be increased as proposed in this protocol.

4. Trial Objectives

4.1 Primary Objective

To assess and compare the effects of a faster (30 ml/kg/day) and a slower (18 ml/kg/day) increase in milk feed volumes on survival of very preterm (<32 weeks) or VLBW (<1,500 g) infants without moderate or severe disability at 24 months of age corrected for prematurity.

4.2 Secondary Objectives

To assess and compare the effects of a faster (30 ml/kg/day) and a slower (18 ml/kg/day) increase in milk feed volumes in very preterm (<32 weeks) or VLBW (<1,500 g) infants with respect to:

- incidence of microbiologically-confirmed or clinically suspected late-onset invasive infection from trial entry until discharged home
- incidence of NEC (Bell stage 2 or 3) from trial entry until discharged home
- time taken to reach full milk feeds (tolerating 150 ml/kg/day for 3 consecutive days)
- growth (weight and head circumference) when discharged home
- duration of parenteral feeding before discharged home
- length of time in intensive care
- length of hospital stay
- diagnosis of cerebral palsy by a doctor or other health professional (parent reported)

5. Trial Design

5.1 Summary

A multi-centre randomised controlled parallel-group trial with an integrated economic evaluation. The trial will recruit 2,800 infants from approximately 30 neonatal units within the UK and Ireland over 3 years.

5.2 Inclusion Criteria

- Gestational age at birth <32 completed weeks, or birth weight <1,500 g
- The infant is receiving ≤30 ml/kg/day of milk at randomisation
- Written informed parental consent is obtained

5.3 Exclusion Criteria

- Infants with a severe congenital anomaly
- Infants who, in the opinion of the treating clinician, have no realistic chance of survival
- Infants who are unlikely to be traceable for follow-up at 24 months of age (for example, infants of non-UK residents)

5.4 Setting

Neonatal units in the United Kingdom or Ireland caring for very preterm or VLBW infants. It is possible for an infant to participate in more than one clinical trial, depending on the interventions being given. Trials being run simultaneously in any units will be discussed by the Chief Investigators (CIs) or their delegated representative(s) to agree whether or not joint recruitment is acceptable to both parties. Individual circumstances will also be reviewed if needed on a case-by-case basis, in consultation with the CI of each trial.

5.5 Primary Outcome

The primary outcome will be the proportion of infants surviving without moderate or severe disability at 24 months of age corrected for prematurity. This composite outcome will be determined by confirming that the child is alive or dead using records held and maintained by The Health and Social Care Information Centre and other central UK NHS bodies. For live infants, a parent report questionnaire will be used to assess sensory and gross motor impairment and standardised measures to assess cognitive function in order to identify children with:

- Moderate/severe visual impairment (reduced vision uncorrected with aids; or blind in one eye with good vision in the contralateral eye; or is blind or can perceive light only)
- Moderate/severe hearing impairment (hearing loss corrected with aids; or some hearing loss but not corrected by aids; or is deaf)
- Moderate/severe gross motor impairment (unable to walk independently; or unable to sit independently)
- Moderate/severe cognitive impairment assessed using the Parent Report of Children's Abilities - Revised (PARCA-R), a parent report measure of non-verbal cognitive and language development. Total PARCA-R scores <44 will be used to identify children with moderate/severe cognitive impairment[35]. This questionnaire has been shown to have at least 80% sensitivity and 80% specificity for identifying children with scores <2SD on a Gold Standard development test[35,36].

A child who has any one or more of these impairments will be classified with a moderate/severe disability. Definitions for motor and sensory impairments described above are as defined in the report published by British Association of Perinatal Medicine (BAPM) in 2008[37]. The 24 month results will be used to assess whether longer term outcome measurement at school age is warranted.

5.6 Secondary Outcomes

Secondary outcomes that will be assessed until discharged home are:

- Survival to discharge home
- Microbiologically-confirmed or clinically suspected late-onset invasive infection from trial entry
- NEC (Bell stage 2 or 3) from trial entry
- Time taken to reach full milk feeds (tolerating 150 ml/kg/day for 3 consecutive days)
- Growth (weight and head circumference) when discharged home
- Duration of parenteral feeding
- Length of time in intensive care
- Length of hospital stay
- Diagnosis of cerebral palsy by a doctor or other health professional (parent reported)

In addition, the separate components of the composite primary outcome at 24 months of age corrected for prematurity will be analysed as secondary outcomes individually, namely:

- Survival
- Moderate/severe visual impairment (reduced vision uncorrected with aids; or blind in one eye with good vision in the contralateral eye; or is blind or can perceive light only)

- Moderate/severe hearing impairment (hearing loss corrected with aids; or some hearing loss but not corrected by aids; or is deaf)
- Moderate/severe gross motor impairment (unable to walk independently; or unable to sit independently).
- Moderate/severe cognitive impairment assessed using the Parent Report of Children's Abilities Revised (PARCA-R)

Secondary outcome data will be collected on paper-based forms when discharged home or transferred. This includes new episodes of **microbiologically-confirmed** or **clinically suspected late-onset invasive infection** from trial entry until discharged home (see *Box 1* and *Box 2* for definitions).

Where parents do not return the two year questionnaire, data will be obtained from clinical records held by the Paediatrician, Health Visitor or GP.

Box 1: Definition of Microbiologically-confirmed Late-onset Invasive Infection

A modified version of the UK Neonatal Infection Surveillance Network case-definition will be used[38,39]:

Microbiological culture from blood or CSF sampled aseptically more than 72 hours after birth of any of the following:

- *potentially pathogenic bacteria (including coagulase-negative Staphylococci species but excluding probable skin contaminants such as diphtheroids, micrococci, propionibacteria or a mixed flora)*
- *fungi*

AND

Treatment for 5 or more days with intravenous antibiotics after the above investigation was undertaken. If the infant died, was discharged, or was transferred prior to the completion of 5 days of intravenous antibiotics, this condition would still be met if the intention was to treat for 5 or more days.

There is no need to report urinary tract infection unless there is also a positive blood culture.

Box 2: Definition of Clinically Suspected Late-onset Invasive Infection

This is adapted from the European Medicines Agency consensus criteria and the predictive model[38,39]:

Either - absence of positive microbiological culture, OR - culture of a mixed microbial flora or of likely skin contaminants (diphtheroids, micrococci, propionibacteria) only.

AND

Clinician intent to administer intravenous antibiotic treatment for 5 or more days (excluding antimicrobial prophylaxis) for an infant who demonstrates 3 or more of the following clinical or laboratory features of invasive infection:

- increase in oxygen requirement or ventilatory support
- increase in frequency of episodes of bradycardia or apnoea
- temperature instability
- ileus or enteral feeds intolerance and/or abdominal distension
- reduced urine output to <1 mL/kg/hour
- impaired peripheral perfusion (capillary refill time >3 seconds, skin mottling or core-peripheral temperature gap >2°C)
- hypotension (clinician defined as needing volume or inotrope support)
- 'irritability, lethargy or hypotonia' (clinician-defined)
- serum C-reactive protein levels to >15 mg/L or procalcitonin ≥2 mg/mL
- white blood cells count <4 or >20 × 10^9 cells/L or platelet count <100 × 10^9/L
- glucose intolerance (blood glucose <40 mg/dL or >180 mg/dL)
- metabolic acidosis (base excess <-10 mmol/L or lactate >2 mmol/L)

6. Trial Procedures

6.1 Informed Consent

Written consent will be sought from the parents only after they have been given a full verbal explanation and written description (via the parent information leaflet [PIL]) of the trial. Parents who do not speak English will only be approached if an adult interpreter is available. Relatives may not interpret.

Informing potential trial participants' parents of possible benefits and known risks will occur as a staged process[40]. If it is likely that the expected infants may be eligible to participate in the trial, introductory verbal and written information will be offered prior to birth. Further information will be provided after birth similarly to the parents of infants not identified before birth. This information will be available both at participating centres and at local hospitals that routinely refer expectant mothers and/or infants into the participating centres.

Written informed parental consent will be obtained by means of dated parental signature and the signature of the person who obtained informed consent; this will be the Principal Investigator (PI) or healthcare professional with delegated authority. A copy of the signed informed consent form (ICF) will be given to the parent(s). A further copy will be retained in the infant's medical notes, a copy will be retained by the PI, and the original will be sent to the SIFT Coordinating Centre.

At all stages it will be made clear to the parents that they remain free to withdraw their infant from the trial at any time without the need to provide any reason or explanation. Parents will be made aware that this decision will have no impact on any aspect of their infant's continuing care.

6.2 Remuneration

Parents will not be given any financial or material incentive or compensation for enrolling their babies in this trial.

6.3 Trial Interventions

The interventions to be studied are two different speeds of increasing milk feeds which are based on survey data indicating acceptable limits of current clinical practice. The two speeds will be: faster (30 ml/kg/day) and slower (18 ml/kg/day). If milk volume is increased as intended, full milk feeds (tolerating 150 ml/kg/day for 3 consecutive days) will be reached 4 days sooner in the faster group. All other aspects of care will remain at the discretion of the responsible neonatal team.

To deliver the intervention, units will prescribe the total volume for the day using the appropriate increment (e.g. from 60 ml/kg up to 90 ml/kg) for the infant's current weight and divide this by the milk feeds given in that 24 hour period. In order to facilitate the ease of measuring milk volumes, rounding to the nearest 0.5 ml of milk for each feed volume will be acceptable. For example a feed of 12.7 ml would be rounded to 12.5 ml.

The daily increments are detailed in *Appendix 1* according to the daily rate of feed increase and the frequency of feeds (hourly or 2 hourly).

An online calculator has been generated by the National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU) to assist with feed calculations.

6.4 Other Medication

The SIFT trial does not involve an Investigational Medicinal Product (IMP). Medication given as part of normal clinical care may be administered without restriction at the discretion of the prescribing clinician. Participation in SIFT does not preclude enrolment in other interventional studies, including Clinical Trials of IMPs.

6.5 Stopping or Modifying the Trial Intervention

Deviations from the scheduled speed of increase may be made at the discretion of the treating clinician if the infant appears unable to tolerate the allocated speed of milk feed increase; such cases will be recorded.

6.6 Randomisation

After consent is obtained, randomisation will take place at the time the clinician is ready to start increasing the feed volume.

Web-based randomisation will be performed via a secure website with a telephone backup available 24/7 (365 days a year) hosted by the NPEU CTU, University of Oxford. Randomisation will ensure balance on important prognostic factors using a minimisation algorithm to including the following factors: collaborating hospital, single or multiple birth, gestational age at birth, and birth weight less than the 10th centile for gestational age. Multiple births will be given the same allocation.

The Senior Trials Programmer at the NPEU CTU will write, test, implement, support, maintain, and monitor the randomisation program and will be custodian of the code.

6.7 Allocation Concealment

Allocations will be concealed by using a secure web-based system and a minimisation algorithm that prospectively produces the allocations i.e. the users of the system will have no insight into the next allocation.

6.8 Blinding

This is an open-label trial; blinding of the clinicians, nursing staff, and parents is not possible. A blinded endpoint review committee will be set up to examine the relevant data collection forms (DCFs) and, if necessary, the clinical notes of a 10% random sample of infants classified as having microbiologically-confirmed or clinically suspected late-onset invasive infection. This review will attempt to determine if there is significant variation between individual consultants and units. The possibility of inconsistent classification between suspected sepsis and NEC that does not require a laparotomy will also be considered as both can have similar presentations and clinical signs, and the committee may be asked to undertake further review.

6.9 Withdrawal from the Trial Intervention

If parents choose to withdraw their infant from receiving the allocated intervention, they will be asked for permission for us to complete data collection and/or follow-up.

The attending clinician may withdraw the infant from treatment if they consider this to be in the best interest of the infant's health and well-being.

6.10 Inter-hospital Transfers

Participating neonatal units will be either:

1. A recruiting site where parental consent is obtained and infants may be recruited, randomised, and commence participation in the trial
2. A continuing care site where the allocated speed of milk feed increase will continue to be administered and routine data collected if a participating infant is transferred in from a recruiting site

From recent experience, about 50% of participating infants are likely to be transferred from their recruiting neonatal care unit to a continuing care site.

6.11 Structure and Duration of Trial

The trial aims to recruit 2,800 infants from approximately 30 neonatal units within the UK and Ireland over a period of 3 years. However, the total duration of the trial will be longer as institutional approval and training will have to take place before recruiting can commence and the last neurodevelopmental follow-up will be the latest date any infant reaches 24 months of age corrected for prematurity.

6.12 Data Collection before Discharge

All of the outcome data for this trial are routinely recorded clinical items that can be obtained from the clinical notes or local microbiological laboratory records. No additional blood or tissue samples are required for this trial. Clinical information will be collected using the following DCFs:

- Trial Entry Form
- Daily Feed Log
- Late-onset Invasive Infection Form
- Gut Signs Form
- Transfer & Discharge Form
- Serious Adverse Event (SAE) Form

Transfer packs will accompany infants to every hospital they are transferred to when possible or provided by the SIFT Coordinating Centre otherwise.

6.13 Data Collection after Discharge

- Parent questionnaire at 24 months of age corrected for prematurity for neurodevelopmental outcomes and health care costs. Where parents do not return the questionnaire, data will be obtained from clinical records held by the Paediatrician, Health Visitor or GP.
- Unit costs will be obtained from published sources and centres participating in the trial. Published sources that will be consulted will include:
    - Unit Costs of Health and Social Care[41]
    - NHS Reference Costs

A trial to investigate the costs of different levels of neonatal intensive care has already been carried out and other cost studies with relevant costs and costs associated with preterm delivery are available to supplement these[42,43]. Costs used in other relevant published sources will be sought for use in sensitivity analysis.

6.14 Economic Data Collection

Cost Data Collection

Relevant resource use data collection will be undertaken prospectively from centres participating in the trial. The process of collecting resource use data will be undertaken separately from data collection on unit costs.

The main resource use to be monitored prior to discharge include the following:

1. Duration of infant stay in hospital differentiated by level of care required such as length of time in intensive care and length of hospital stay
2. Duration of parenteral feeding before discharged home
3. Antibiotic usage
4. Any additional procedures required or associated with adverse events, for example

Parents will be asked about travel costs and other related costs (such as time off work) associated with outpatient visits or other admission to hospital for the infant in a questionnaire sent at 24 months of age corrected for prematurity. This model has been used successfully in the BOOST-II UK Trial.

Unit costs will be obtained and attached to resource items in order that a cost can be calculated for item of resource. Unit costs will be obtained from published sources and centres participating in the trial. Published sources will include Unit Costs of Health and Social Care[41] and NHS Reference Costs. Many cost data are already available in recently published sources. A study to investigate the costs of different levels of neonatal intensive care has already been carried out and other cost studies with relevant costs and costs associated with preterm delivery are available to supplement these. Costs used in other relevant published sources will be sought for use in sensitivity analysis.

Given the objective of the trial and the duration of follow-up, only a within trial economic analysis will be carried out. A preliminary cost consequence analysis compares all costs and outcomes for the intervention and current practice in a disaggregated format. The main economic analysis will be in the form of a cost-effectiveness analysis based on an intermediate outcome of cost per neonatal sepsis avoided when discharged home and on the outcome of disability-free survival at 24 months of age corrected for prematurity (cost per additional survivor without disability at 24 months of age corrected for prematurity).

The analysis will adopt an incremental approach in that data collection will concentrate on resource use and outcome differences between trial arms. As the majority of cost data are skewed, in particular days in hospital before being discharged home, and the mean cost of each procedure is of importance, a bootstrapping approach will be undertaken in order to calculate confidence intervals around the mean costs[44,45]. The recommended approach to discounting will be followed if necessary, which would include discounting costs and benefits as per NICE guidelines at 3.5%.

Results will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value where appropriate. Uncertainty in the confidence to be placed on the results of the economic analysis will be explored by estimating. These plot the probability that the intervention is cost-effective against threshold values for cost-effectiveness. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial based data itself, the methods employed to analyse the data and the generalisability of the results to other settings.

6.15 End of Trial

SIFT has two phases: an intervention phase and a follow-up phase. The end of the intervention phase will be when the last participating infant has been discharged home or dies in hospital. NHS Trusts will be notified of the end of trial for their records. The end of the follow-up phase will be the latest date any participating infant reaches 24 months of age corrected for prematurity. The REC and Sponsor will be notified at this point.

6.16 Early Cessation

Taking into consideration interim data and other evidence from relevant studies or meta-analyses, the Data Monitoring Committee (DMC) may recommend that the Trial Steering Committee (TSC) terminate the trial, if in its view, there is proof beyond reasonable doubt that the data indicate that the trial recruitment should be terminated for all infants or for a particular subgroup of infants. Guidelines for early cessation will be agreed with the DMC and documented in the DMC Charter[46].

6.17 Follow-up

A parent questionnaire will be sent out by the NPEU CTU, which will include the PARCA-R.

7. Safety reporting

7.1 Definitions

7.1.1 Serious Adverse Event (SAE)

Adverse events are defined as serious if they:

- Result in death
- Are life-threatening
- Require inpatient hospitalisation or prolongation of existing hospitalisation
- Result in persistent or significant disability/incapacity, or
- Are a congenital anomaly/birth defect

The term “life-threatening” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

SAEs are to be reported from randomisation until discharged home.

7.1.2 Expected Serious Adverse Events

The following are SAEs that could be reasonably expected to occur in this population of infants during the course of the trial or form part of the outcome data. They do not require reporting by the SIFT Coordinating Centre as SAEs:

- Death (unless unexpected in this population)
- NEC or focal intestinal perforation
- Microbiologically-confirmed or clinically suspected late-onset invasive infection
- Bronchopulmonary dysplasia (mechanical ventilator support or supplemental oxygen at 36 weeks’ post menstrual age)
- Intracranial abnormality (haemorrhage, parenchymal infarction, or white matter damage) on cranial ultrasound scan or other imaging
- Pulmonary haemorrhage
- Patent ductus arteriosus requiring treatment (non-steroidal anti-inflammatory drugs or surgery)
- Retinopathy of prematurity

7.2 Reporting Procedures

All expected SAEs (described above) will be recorded on the DCFs and will be reviewed by the DMC at regular intervals throughout the trial.

Any unexpected SAEs will be reported by trial sites to the SIFT Coordinating Centre as soon as possible after the event has been recognised as an SAE that is not included in the list of expected SAEs. All SAE information must be recorded on an SAE reporting form and faxed to the SIFT Coordinating Centre. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form and faxed to the SIFT Coordinating Centre. A Standard Operating Procedure (SOP) outlining the reporting procedure for clinicians will be provided with the SAE form and in the trial handbook. The SIFT Coordinating Centre will process and report the event as specified in its own SOPs.

The CI will inform all investigators concerned of relevant information about unexpected SAEs that could adversely affect the safety of participants. The CI shall submit, once a year throughout the recruiting period of the trial, or on request, a safety report to the Ethics Committee and the sponsor.

8. Statistics and Analysis

8.1 Sample Size

The primary comparison will be the difference in the proportion of infants surviving without moderate or severe disability at 24 months of age corrected for prematurity. Based on previous trials, it is estimated that 80% of the infants will survive to two years, and that 11% of these will have a moderate or severe impairment[14]. Hence it is estimated the proportion surviving without moderate or severe disability in the control group receiving the 18 ml/kg/day increment will be 71%. With a total sample size of 2,500 and allowing for a response rate of 80%, there will be 90% power to detect an absolute difference of 6.3% (from 71.0% in the control group to 77.3%) in this proportion, with a two-sided 5% significance level.

With the same level of significance, a sample size of 2,500 infants will have 90% power to detect an absolute risk difference of 5.4% (from 25.0% in control group to 19.6%) in the incidence of sepsis[47], and an absolute risk difference of 3.5% (from 6.0% in control group to 9.5%) in the incidence of NEC (Bell stage 2 or 3)[48–50].

However, the original sample size of 2,500 infants was calculated based on individual randomisation. During the development of the randomisation procedures, parent representative groups including TAMBA (Twins And Multiple Births Association), BLISS (National Charity for the Newborn), and SSNAP (an Oxford-based charity providing support for the sick newborn and their parents) were approached, to ascertain if parents had a preference to their babies receiving the same allocation, as opposed to possibly receiving a different allocation from each other. The unanimous verdict was that it was important that multiple births should be given the same allocation and that otherwise, this may be a barrier to recruitment, given that the intervention could not be blinded.

Therefore an approach that multiple births would receive the same allocation was adopted. This has implications for sample size since multiple births are genetically identical for identical multiples and genetically very similar for non-identical multiples, and so there is a need to allow for the increased likelihood of their outcomes being correlated.

In consultation with the independent Data Monitoring and the Trial Steering Committees, a decision was made to increase the sample size from 2,500 to 2,800 infants. This is based on the multiple birth rate of 25% observed in the first interim analysis and an intracluster correlation between 0.8 to 0.9, obtained from the Late and Moderate preterm Birth Study (unpublished data) multiples assessed at 2 years of age using the PARCA-R.

8.2 Statistical Analysis

Demographic factors and clinical characteristics will be summarised with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile [IQR] or entire range) for other continuous variables.

Infants will be analysed according to allocation regardless of the speed of milk feed increase they actually received. For the incidence of sepsis, NEC, and survival without moderate or severe disability at 24 months of age corrected for prematurity, risk ratios and 95% confidence intervals will be calculated (99% CI for other dichotomous outcomes). For normally distributed continuous outcomes, the mean difference (99% CI) will be presented, and the median difference (99% CI) for skewed continuous variables. Kaplan-Meier plots will be presented for time to event outcomes such as time to reach full milk feeds, and analysed using the log rank test.

The two groups will be compared using generalised estimating equations, adjusting for the minimisation factors to account for the correlation between treatment groups introduced by balancing the randomisation (which forces outcomes between treatment arms to be similar apart from any treatment effect)[51]. Both the crude unadjusted and adjusted estimates will be presented, but the primary inference will be based on the adjusted analysis. This method of analysis will also account for the correlation in outcomes between twins and siblings born in a subsequent pregnancy during the trial period. Adjusted risk ratios will be estimated using a log binomial regression model, or using a log poisson regression model with a robust variance estimator if the binomial model fails to converge[52]. Linear regression will be used for normally distributed outcomes, quantile regression for skewed continuous variables, and Cox regression for time to event outcomes. The impact of non-response and missing data at 2 years follow-up will be examined in a sensitivity analysis.

The consistency of the effect of advancing milk feeds across specific subgroups of infants will be assessed using the statistical test of interaction. Pre-specified subgroup analyses include: (i) week of gestation at birth, (ii) birth weight (<10th centile for gestational age versus >=10th centile and (iii) type of milk (breast milk only/formula only/mixed). Subgroup analysis will be performed on the primary outcome, and the incidence of sepsis and NEC.

8.3 Economic Analysis

It is planned to determine the relative cost-effectiveness of the alternative rates of milk feed increases. The economic evaluation will be carried out from two perspectives: first from the perspective of the NHS, which will include the direct costs and outcomes to the NHS for the duration of the trial. These will consist of costs that are incurred during the initial hospital stay and those that occur after being

discharged home until 24 months of age corrected for prematurity. Secondly the perspective will be extended to include the private out-of-pocket costs to the families associated with travel and time off work during the period of follow-up.

9. Direct Access to Source Data/Documents

Direct access will be granted to authorised representatives from study organisers, the research sponsor and NHS Trusts/NHS Boards/Health and Social Care Trusts to permit trial-related monitoring, audits, and inspections..

10. Quality Control and Assurance

10.1 Site Initiation and Training

The Local Research Nurses (LRNs) will be trained in the protocol and in conjunction with the local PI deliver this training to the site nurses to make sure that they are conversant with the trial's procedures. They will also promote the trial so that the necessary recruitment targets are reached within the timescale taking primary responsibility for educating clinicians about the trial, for maintaining enthusiasm, and encouraging recruitment in their participating centre. The LRN will act as the point of contact for the SIFT Coordinating Centre and will troubleshoot as the need arises.

10.2 Data Collection and Processing

All trial data will be collected using bespoke DCFs. Data will be processed in line with the NPEU CTU Data Management SOPs, using validated data management systems to ensure consistency, viability, and quality of the data. It will be stored in line with the Data Protection Act (1998).

10.3 Central Statistical Monitoring

Central statistical monitoring will be used at NPEU CTU to monitor patterns of recruitment at sites and within the data; outlier data will be investigated and may trigger 'for cause' site monitoring.

The Head of Trials and the Senior Trials Programmer will develop an appropriate central monitoring plan for the trial and review the output to identify any unexpected patterns or problems. The Head of Trials will decide if any action needs to be taken.

10.4 Site Monitoring and Auditing

The LRN will be responsible for the day-to-day smooth running of the trial at a recruiting site. They will encourage recruitment, provide staff education and training, and monitor data collection completeness and quality.

The LRN will submit formal site visit reports to the Project Management Group (PMG). No other routine monitoring will be carried out unless the central monitoring exercises raise cause for concern. Likewise, sites will only be audited if central monitoring indicates a necessity.

10.5 Risk Assessment

Prior to trial commencement, the NPEU CTU performed a risk assessment of the trial that will be reviewed at regular intervals according to its own SOP. This trial is a comparison of standard treatments, which does not include a drug treatment, so does not fall under the auspices of the MHRA. Based on the assessment, this trial poses minimal risk, no greater than normal care within a neonatal intensive care unit, to either the participants or the health care professionals delivering the intervention.

10.6 National Registration Systems

All surviving infants recruited into SIFT will be 'flagged' after being discharged home to confirm status using records held and maintained by the The Health and Social Care Information Centre and other central UK NHS bodies.

11. Ethics

11.1 Good Clinical (Research) Practice

The trial will be conducted according to the principles of:

- The Declaration of Helsinki (amended 2008)
- The International Conference of Harmonisation guidelines for Good Clinical Practice (E6)

11.2 Independent Research Ethics Committee (REC)

The trial will only start after gaining approval from a National Research Ethics Service (NRES) registered ethics committee. Additionally, approval of the NHS Trust Research and Development (R&D) Office will be sought for individual trial sites.

Applications will be submitted through the Integrated Research Application System (IRAS).

A copy of the protocol, PIL, and ICF will be submitted to the REC for approval.

The CI or their delegate will submit and, where necessary, obtain approval from the REC for any protocol amendments and changes to the informed consent document.

The CI or their delegate will notify any protocol deviations to the sponsor and will notify the REC of these in accordance with local procedures.

11.3 Participant Confidentiality, Data Handling and Record Keeping

SOPs are in place for the collection and handling of data received at the SIFT Coordinating Centre at the NPEU CTU. The CI will take overall responsibility for ensuring that each participant's information is kept confidential. All paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998). Data collected on the DCFs will be transferred for storage in an electronic database in which the participant will be identified only by a trial specific number. The infant's name and any other identifying details will be stored in a separate database linked only by the trial number. This information will be collected and retained with the parent's explicit consent to enable follow-up to be undertaken. After the trial has been completed and the reports published, the data will be archived in a secure physical and electronic location with controlled access.

Storage will be on a restricted area of a file server. The server is in a secure location and access is restricted to a few named individuals. Access to the building in which NPEU is situated is via an electronic tag and individual rooms are kept locked when unoccupied. Authorisation to access restricted areas of the NPEU network is as described in the NPEU security policy.

Data will be processed on a workstation by authorised staff. The workstations access the network via a login name and password (changed regularly). No data are stored on individual workstations. Backing up is done automatically overnight to an offsite storage area. The location of the back-up computer is in a separate department which has electronic tag access. Access to the room in which the back-up machine is located is via a key-pad system.

Unidentifiable data from this study may be shared with other groups who are carrying out similar work.

11.4 Retention of Personal Data

Data will be retained according to NHS guidelines, which recommend that data collected from children is retained until at least the child's 25th birthday. At this point the further retention of the data will be reviewed in line with the appropriate data protection guidelines.

12. Funding

The National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme is funding the trial.

13. Insurance

The University of Oxford's Clinical Trials, Professional Negligence, and Public Liability Insurances are arranged through Lloyds Market. It is the University's present intention to keep this arrangement, or alternative arrangements with similar Terms and Conditions in place, for the foreseeable future. The University reserves the right to place other alternative risk transfer mechanisms in place, and which will provide a level of cover in line with those presently arranged through the insurance market.

Indemnity will be provided against both negligent and non-negligent harm as defined below:

- Negligent Harm: The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment which is provided.
- Non-Negligent Harm: The University has arrangements in place to provide for non-negligent harm arising from participation in the study for which the University is the Research Sponsor.

14. Trial Governance

14.1 Site Research and Development Approval

Individual sites will only commence recruiting participants once they receive approval from NHS Trust R&D Offices. Applications to NHS Trust R&D Offices will be submitted through the NIHR Coordinated System for gaining NHS Permission.

14.2 Trial Sponsor

The University of Oxford is the nominated sponsor for the trial.

14.3 Coordinating Centre

The SIFT Coordinating Centre will be at the NPEU CTU, University of Oxford where the Trial Coordinator will be based. The NPEU CTU will be responsible for all trial programming, randomisation, data entry and management, conducting statistical analyses, servicing both the DMC and TSC, and, in collaboration with the CI and the Trial Research Nurse, for the day-to-day running of the trial including recruitment of centres and training of staff.

14.4 Project Management Group (PMG)

The trial will be supervised on a day-to-day basis by the PMG. This group reports to the TSC which is responsible to the trial sponsor. At each participating centre, a local PI will report to the PMG via the project funded staff based at the NPEU CTU.

The core PMG will consist of Jon Dorling (Chief Clinical Investigator) and NPEU CTU staff including:

- CTU Director
- Senior Trials Manager
- Senior Trials Programmer
- Quality Assurance Manager
- Trial Coordinator
- Trial Statistician
- Trial Programmer

- Administrator/Data Manager

The core PMG will meet regularly (at least monthly).

Every 3–4 months the Clinical Investigators' Group, (CIG) will meet. This will comprise all members of the co-applicant group and the members of the core PMG.

14.5 Trial Steering Committee (TSC)

The trial will be overseen by a TSC consisting of an independent chair and at least two other independent members.

Representatives from relevant Patient/Public Involvement groups and the CI will be joined by observers from the NPEU CTU. The HTA programme manager will be invited to attend all TSC meetings.

14.6 Data Monitoring Committee (DMC)

A DMC independent of the applicants and of the TSC will review the progress of the trial at least annually and provide advice on the conduct of the trial to the TSC and (via the TSC) to the HTA programme manager.

14.7 Competing Interests

In 2011 Dr Embleton provided advice to Baxter, a company who make parenteral nutrition solutions for neonates. The honoraria received was donated to charity. He has no ongoing relationships with this or any other relevant commercial organisation and does not disclose any other relevant conflicts of interest.

The SIFT Investigators confirm that they have no other competing interests or affiliations to declare.

15. Communication

15.1 Protocol

After REC approval has been obtained, this protocol will be submitted for publication and will be available for download via the NPEU website.

15.2 Post-recruitment Information for Parents and 'On-going Consent'

Parents will be offered an early appointment with the PI or delegated deputy to ensure they understand the trial procedures and continue to consent to participate in the trial.

15.3 Post-discharge Information

Information about the trial will continue to be offered to parents after their infant leaves the neonatal unit. A regular newsletter will be produced giving parents information about the trial until it has finished. Experience with other studies in this area suggests that parents of infants who die may want to receive these newsletters, and all parents will be offered the chance to receive correspondence or opt out.

15.4 Trial Findings

The CI and NPEU CTU will coordinate dissemination of the results from this trial. All publications using data from this trial to undertake original analyses will be submitted to the TSC for review before release. To safeguard the scientific integrity of the trial, data from this trial will not be presented in public before the main results are published without the prior consent of the TSC.

15.5 Publication Policy/Acknowledgement of Contribution

The success of the trial depends on a large number of neonatal nurses, neonatologists, and parents. Credit for the trial findings will be given to all who have collaborated and participated in the trial including all local coordinators and collaborators, members of the trial committees, the SIFT Coordinating Centre, and trial staff. Authorship at the head of the primary results paper will take the form "Speed of Increasing

milk Feeds Trial (SIFT) Collaborative Group" to avoid giving undue prominence to any individual. The writing will be the responsibility of a writing committee including all of the investigators. All contributors to the trial will be listed at the end of the report, with their contribution to the trial identified.

It is the intention of the SIFT group to publish the protocol, and two peer-reviewed articles detailing (i) the analysis of key short-term outcomes including the incidence of microbiologically-confirmed or clinically suspected late-onset invasive infection from trial entry until discharged home and the incidence of NEC (Bell stage 2 or 3), and (ii) long-term outcomes including survival without moderate or severe disability at 24 months of age corrected for prematurity.

Those responsible for other publications reporting specific aspects of the trial, such as detailed microbiological outcomes, may wish to utilise a different authorship model, such as "[name], [name] and [name] on behalf of the 'The SIFT Collaborative Group'". Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and the TSC.

Parents will be sent a summary of trial publications if they wish, which will contain full references.

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17. Appendix 1 – Feeding Schedules

FASTER MILK FEED INCREASE (30 ml/kg/day increment on HOURLY feeds)

Working weight between							
350	&	**362**	g increase hourly milk feed volume by	**0.5 ml**	every	**27**	hours
363	&	**376**	g increase hourly milk feed volume by	**0.5 ml**	every	**26**	hours
377	&	**391**	g increase hourly milk feed volume by	**0.5 ml**	every	**25**	hours
392	&	**408**	g increase hourly milk feed volume by	**0.5 ml**	every	**24**	hours
409	&	**426**	g increase hourly milk feed volume by	**0.5 ml**	every	**23**	hours
427	&	**446**	g increase hourly milk feed volume by	**0.5 ml**	every	**22**	hours
447	&	**468**	g increase hourly milk feed volume by	**0.5 ml**	every	**21**	hours
469	&	**492**	g increase hourly milk feed volume by	**0.5 ml**	every	**20**	hours
493	&	**518**	g increase hourly milk feed volume by	**0.5 ml**	every	**19**	hours
519	&	**548**	g increase hourly milk feed volume by	**0.5 ml**	every	**18**	hours
549	&	**581**	g increase hourly milk feed volume by	**0.5 ml**	every	**17**	hours
582	&	**619**	g increase hourly milk feed volume by	**0.5 ml**	every	**16**	hours
620	&	**662**	g increase hourly milk feed volume by	**0.5 ml**	every	**15**	hours
663	&	**711**	g increase hourly milk feed volume by	**0.5 ml**	every	**14**	hours
712	&	**767**	g increase hourly milk feed volume by	**0.5 ml**	every	**13**	hours
768	&	**834**	g increase hourly milk feed volume by	**0.5 ml**	every	**12**	hours
835	&	**914**	g increase hourly milk feed volume by	**0.5 ml**	every	**11**	hours
915	&	**1000**	g increase hourly milk feed volume by	**0.5 ml**	every	**10**	hours
1001	&	**1037**	g increase hourly milk feed volume by	**1 ml**	every	**19**	hours
1038	&	**1097**	g increase hourly milk feed volume by	**1 ml**	every	**18**	hours
1098	&	**1163**	g increase hourly milk feed volume by	**1 ml**	every	**17**	hours
1164	&	**1238**	g increase hourly milk feed volume by	**1 ml**	every	**16**	hours
1239	&	**1324**	g increase hourly milk feed volume by	**1 ml**	every	**15**	hours
1325	&	**1422**	g increase hourly milk feed volume by	**1 ml**	every	**14**	hours
1423	&	**1535**	g increase hourly milk feed volume by	**1 ml**	every	**13**	hours
1536	&	**1669**	g increase hourly milk feed volume by	**1 ml**	every	**12**	hours
1670	&	**1828**	g increase hourly milk feed volume by	**1 ml**	every	**11**	hours
1829	&	**2021**	g increase hourly milk feed volume by	**1 ml**	every	**10**	hours
2022	&	**2258**	g increase hourly milk feed volume by	**1 ml**	every	**9**	hours
2259	&	**2560**	g increase hourly milk feed volume by	**1 ml**	every	**8**	hours
2561	&	**2953**	g increase hourly milk feed volume by	**1 ml**	every	**7**	hours
2954	&	**3000**	g increase hourly milk feed volume by	**1 ml**	every	**6**	hours

SLOWER MILK FEED INCREASE (18 ml/kg/day increment on HOURLY feeds)

Working weight between							
350	&	355	g increase hourly milk feed volume by	0.25 ml	every	23	hours
356	&	372	g increase hourly milk feed volume by	0.25 ml	every	22	hours
373	&	390	g increase hourly milk feed volume by	0.25 ml	every	21	hours
391	&	410	g increase hourly milk feed volume by	0.25 ml	every	20	hours
411	&	432	g increase hourly milk feed volume by	0.25 ml	every	19	hours
433	&	457	g increase hourly milk feed volume by	0.25 ml	every	18	hours
458	&	484	g increase hourly milk feed volume by	0.25 ml	every	17	hours
485	&	516	g increase hourly milk feed volume by	0.25 ml	every	16	hours
517	&	551	g increase hourly milk feed volume by	0.25 ml	every	15	hours
552	&	592	g increase hourly milk feed volume by	0.25 ml	every	14	hours
593	&	639	g increase hourly milk feed volume by	0.25 ml	every	13	hours
640	&	695	g increase hourly milk feed volume by	0.25 ml	every	12	hours
696	&	700	g increase hourly milk feed volume by	0.25 ml	every	11	hours
701	&	711	g increase hourly milk feed volume by	0.5 ml	every	23	hours
712	&	744	g increase hourly milk feed volume by	0.5 ml	every	22	hours
745	&	780	g increase hourly milk feed volume by	0.5 ml	every	21	hours
781	&	820	g increase hourly milk feed volume by	0.5 ml	every	20	hours
821	&	864	g increase hourly milk feed volume by	0.5 ml	every	19	hours
865	&	914	g increase hourly milk feed volume by	0.5 ml	every	18	hours
915	&	969	g increase hourly milk feed volume by	0.5 ml	every	17	hours
970	&	1032	g increase hourly milk feed volume by	0.5 ml	every	16	hours
1033	&	1103	g increase hourly milk feed volume by	0.5 ml	every	15	hours
1104	&	1185	g increase hourly milk feed volume by	0.5 ml	every	14	hours
1186	&	1279	g increase hourly milk feed volume by	0.5 ml	every	13	hours
1280	&	1391	g increase hourly milk feed volume by	0.5 ml	every	12	hours
1392	&	1523	g increase hourly milk feed volume by	0.5 ml	every	11	hours
1524	&	1684	g increase hourly milk feed volume by	0.5 ml	every	10	hours
1685	&	1882	g increase hourly milk feed volume by	0.5 ml	every	9	hours
1883	&	2133	g increase hourly milk feed volume by	0.5 ml	every	8	hours
2134	&	2461	g increase hourly milk feed volume by	0.5 ml	every	7	hours
2462	&	2909	g increase hourly milk feed volume by	0.5 ml	every	6	hours
2910	&	3000	g increase hourly milk feed volume by	0.5 ml	every	5	hours

FASTER MILK FEED INCREASE (30 ml/kg/day increment on 2 HOURLY feeds)

Working weight between							
350	&	369	g increase two-hourly milk feed volume by	0.5 ml	every	14	hours
370	&	436	g increase two-hourly milk feed volume by	0.5 ml	every	12	hours
437	&	533	g increase two-hourly milk feed volume by	0.5 ml	every	10	hours
534	&	650	g increase two-hourly milk feed volume by	0.5 ml	every	8	hours
651	&	738	g increase two-hourly milk feed volume by	1 ml	every	14	hours
739	&	872	g increase two-hourly milk feed volume by	1 ml	every	12	hours
873	&	1000	g increase two-hourly milk feed volume by	1 ml	every	10	hours
1001	&	1107	g increase two-hourly milk feed volume by	1.5 ml	every	14	hours
1108	&	1309	g increase two-hourly milk feed volume by	1.5 ml	every	12	hours
1310	&	1500	g increase two-hourly milk feed volume by	1.5 ml	every	10	hours
1501	&	1745	g increase two-hourly milk feed volume by	2 ml	every	12	hours
1746	&	2133	g increase two-hourly milk feed volume by	2 ml	every	10	hours
2134	&	2742	g increase two-hourly milk feed volume by	2 ml	every	8	hours
2743	&	3000	g increase two-hourly milk feed volume by	2 ml	every	6	hours

SLOWER MILK FEED INCREASE (18 ml/kg/day increment on 2 HOURLY feeds)

Working weight between								
350	&	**380**	g increase two-hourly milk feed volume by	**0.5 ml**	every	**22**	hours
381	&	**421**	g increase two-hourly milk feed volume by	**0.5 ml**	every	**20**	hours
422	&	**470**	g increase two-hourly milk feed volume by	**0.5 ml**	every	**18**	hours
471	&	**533**	g increase two-hourly milk feed volume by	**0.5 ml**	every	**16**	hours
534	&	**615**	g increase two-hourly milk feed volume by	**0.5 ml**	every	**14**	hours
616	&	**700**	g increase two-hourly milk feed volume by	**0.5 ml**	every	**12**	hours
701	&	**761**	g increase two-hourly milk feed volume by	**1 ml**	every	**22**	hours
762	&	**842**	g increase two-hourly milk feed volume by	**1 ml**	every	**20**	hours
843	&	**941**	g increase two-hourly milk feed volume by	**1 ml**	every	**18**	hours
942	&	**1066**	g increase two-hourly milk feed volume by	**1 ml**	every	**16**	hours
1067	&	**1230**	g increase two-hourly milk feed volume by	**1 ml**	every	**14**	hours
1231	&	**1454**	g increase two-hourly milk feed volume by	**1 ml**	every	**12**	hours
1455	&	**1777**	g increase two-hourly milk feed volume by	**1 ml**	every	**10**	hours
1778	&	**2285**	g increase two-hourly milk feed volume by	**1 ml**	every	**8**	hours
2286	&	**3000**	g increase two-hourly milk feed volume by	**1 ml**	every	**6**	hours

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