Rapid versus slow advancement of feeds for enterally fed extremely low birth weight infants ≤ 1000 g: a randomised controlled trial

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DECLARATION

I, Moegammad Shukri Raban, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

This work has not been reported or published prior to registration for the degree, Master of Philosophy in Neonatology.

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……. ……

Dr Moegammad Shukri Raban Date

This dissertation is submitted with the approval of the following supervisors:

……. ……..

A/Prof Michael C Harrison Date

…….. ……..

A/Prof Alan R Horn Date

Dedication

This work is dedicated to my wife, Majedah; sons, Maahir and Mujaahid and daughter, Thanaa.

Thank you for your patience and constant encouragement.

Acknowledgement

It always seems impossible until it's done – Nelson Mandela addressing a crowd at City Hall, Cape Town, 11 May 1994 after he was elected State President of South Africa.

A study of this nature was never going to be an easy task!

There have been many role players who have helped see this study to fruition, to which I am deeply indebted and thankful for.

I cannot express my deepest thanks to the parents who enrolled their precious babies onto this study. During the toughest times of your lives you saw the potential benefit not only to your but all preterm babies. You provided your babies with lifesaving breast milk and spent hours at their bedsides. I commend and salute you.

The staff of the neonatal unit at Groote Schuur Hospital, you are fantastic.

The consultants in the department of Neonatology at Groote Schuur Hospital and my supervisors; you all contributed to the neonatologist I have become. You allowed me to express myself, discovering my true potential. Thank you for your support, guidance and encouragement whilst embarking on this huge project.

A special thanks to Dr Geoff Moller who acted as the independent supervisor on the trial steering committee, ensuring that safety of the trial participants was not compromised.

My family; you have been the biggest part of my life. Your patience, love and support are evident in this work. To my parents, you have been a constant pillar of strength, support and encouragement in my life. I am forever thankful and grateful.

Lastly, to the Almighty, the accomplishment of this work is only due to You.

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List of abbreviations

BMF	breast milk fortifier
DEBM	pasteurised donor human breast milk
EBM	expressed human breast milk
ELBW	extreme low birth weight infants < 1000 g
KMC	kangaroo mother care
NEC	necrotising enterocolitis
NPO	nil by mouth
PN	parenteral nutrition
RCT	randomised controlled trial
VLBW	very low birth weight infant between 1000 g and 1500 g

Preface

This minor dissertation examines the outcomes of two elements of feeding; the initiation enteral volume and the rate of the enteral advancement volume in infants weighing ≤ 1000 g. The dissertation presents novel data as this sub-group of patients have previously been under- represented in research, and importantly, the study is the first to examine both elements of feeding simultaneously. The dissertation is presented in four parts.

Part A is the research protocol of the study, a 2x2 factorial randomised controlled trial, which was approved by the Department of Paediatrics and Child Health Departmental Research Committee and the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee (HREC ref: 283/2011). The trial is registered with the ISRCTN Register (http://isrctn.org) (identifier ISRCTN96923718).

Part B is a structured literature review of randomised controlled trials examining the effect that the rate of advancement of enteral feeds has on the incidence of morbidity and mortality in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants.

Part C presents the results of the research described in Part A, presented in the form of a manuscript which will be submitted to *Pediatrics* for publication. This is the final version of the manuscript as submitted to the journal. The title of the manuscript differs from that of the original protocol in order for it to capture the extent of the research.

Part D contains supporting documentation.

Abstract

Background

The timeous achievement of full enteral nutrition in a preterm infant is a critical prerequisite for optimal growth, neurodevelopment and long-term wellbeing. However, the optimal enteral feeding regimen for preterm infants has not been established, and wide variations occur in practice.

The debate on the most appropriate feeding strategy is nuanced by studies suggesting that early introduction of enteral feeds and the rapid advancement of enteral feeds may increase the risk of feeding intolerance and may be involved in the pathogenesis of necrotising enterocolitis (NEC).

Objective

1. To review randomised controlled trials (RCT); examining the effect that the rate of advancement of enteral feeds has on the incidence of; NEC, mortality, growth, health care utilisation and other morbidities in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants.

2. To establish the safety and efficacy of commencing enteral breast milk feeds at 24 ml/kg/day on the day of birth and advancing enteral breast milk feeds at 36 ml/kg/day, in infants weighing ≤ 1000 g.

Methods

A research protocol for the 2x2 factorial randomised controlled trial was approved by the Department of Paediatrics and Child Health Departmental Research Committee and the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee (HREC ref: 283/2011). The trial is registered with the ISRCTN Register (http://isrctn.org) (identifier ISRCTN96923718).

A structured literature search was done using the Cochrane database and using Pubmed to search Medline for randomised controlled trials assessing the effect of slow versus faster rates of enteral feed volume advancement on the incidence of NEC.

Results

Literature review

Five randomised controlled trials were identified. None of the trials showed a statistically significant effect of feeding strategy on the risk of NEC or mortality.
All five trials demonstrated that infants randomised to the slow advancement group took statistically significantly longer to establish full enteral feeds and to regain their birth weight.

Randomised controlled trial

The results are presented in Part C in the form of a manuscript as submitted to *Pediatrics* for publication.

Two hundred infants were recruited (51 low/slow, 47 low/rapid, 52 high/slow, 50 high/rapid). Infants on rapid advancement were the quickest to reach a weight of 1500 g, (hazard 2.3, $p = 0.003$, 95% CI 1.3–4.0). Rapid advancement was associated with fewer days to regain birth weight, (hazard 2.3, $p = 0.001$, 95% CI 1.4–3.6) and fewer days in hospital (hazard 1.9, $p = 0.006$, 95% CI 1.2–3.1). There were no significant differences in the rates of NEC, feed intolerance, or late-onset sepsis between the groups.

Conclusion

Literature review

The review suggests that slow advancement of enteral feed volume does not reduce the risk of NEC.

Randomised controlled trial

Higher initiation feed volumes and larger daily feed increments in infants ≤ 1000 g birth weight, was well tolerated, resulted in increased early weight gain and reduced hospital stay. Though the trial had limited power to detect a difference in NEC, no increase was observed with this regimen.

Part A: The Protocol

Plain language synopsis of the protocol

Purpose and Objectives

The optimal enteral feeding regimen has not been established in preterm infants, especially those weighing less than 1000 g; uncertainty exists regarding the timing and volume of the initiation enteral volume and the speed of advancement of enteral feeds.
The aim of the study is to establish the safety and efficacy of commencing enteral milk feeds at 24 ml/kg/day on the day of birth and advancing the enteral feeds at 36 ml/kg/day, in infants with a birth weight ≤ 1000 g.

Methods

Location

The study will be conducted in the tertiary level, neonatal unit at Groote Schuur Hospital in Cape Town, South Africa.

Design

A randomised controlled trial will be conducted using a 2×2 factorial design to assess the higher starting feed volume and faster advancement as separate components.

Outcomes

The primary outcome is the time to attain a weight of 1500 g. This reflects the weight at which infants in our service become eligible for full-time kangaroo mother care (KMC).

Secondary outcomes are: 1) time to regain birth weight; 2) number of feed interruptions; 3) incidence of NEC; 4) mortality rate before discharge; 5) growth in head circumference from birth to discharge; 6) growth in length from birth to discharge; 7) parenteral nutrition utilisation; 8) incidence of late-onset sepsis; and 9) duration of hospital stay.

Recruitment and randomisation

All inborn infants with a birth weight of ≤ 1000 g are eligible for trial entry. All outborn infants are excluded. Infants with any congenital abnormalities; which preclude enteral feeding or are immediately life threatening will also be excluded.

On admission, the recruiting clinician will invite informed written consent from parents of eligible infants for participation in the study. Following consent, the clinician will contact the randomisation service and obtain treatment assignment, which will be to one of four groups:

Low volume initiation and slow advancement;
Low volume initiation and rapid advancement;
High volume initiation and slow advancement;
High volume initiation and rapid advancement.

Randomisation will be performed using a computer-generated random group allocation and be administered by telephone by an investigator, who is off site and blinded to the infants' clinical details at study entry. Randomisation will be performed according to gender and weight stratification into two groups: < 700 g and 701–999 g.

Safety monitoring

Adverse Reactions (AR)

An adverse reaction (AR) is defined as any untoward or unintended response related to trial intervention. Adverse reactions will be recorded. In the event that an AR is reported during the trial, investigators will assess the severity of the adverse event using the following criteria, detailed on the adverse event case report form (CRF).

- **Mild:** Awareness of signs or symptoms; but easily tolerated; of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication.
- **Moderate:** Discomfort severe enough to cause interference with usual infant activities.
- **Severe:** Inability to carry out usual infant activities; signs and symptoms may be of systemic nature or require medical evaluation and/or treatment.

Specific Adverse Events

Both feeding regimens are used in current clinical practice.

The following specific adverse events will be recorded:

- Episodes of feeds being stopped due to feed intolerance based on pre-defined criteria
- Culture positive sepsis (based on pre-defined criteria) while on parenteral nutrition
- Necrotising enterocolitis based on pre-defined criteria
- Complications relating to percutaneous catheters

Serious Adverse Events/Reactions

All serious adverse reactions will be reported to the trial co-ordinator. Serious adverse events (SAE) or reactions can be defined as any untoward medical occurrence or effect that:

- results in death
- is life-threatening
- prolongs hospitalisation
- results in persistent or significant disability or incapacity

Expected SAEs/clinical outcomes due to preterm birth

There are multiple serious complications that could occur as a consequence of preterm birth. It will be at the judgement of the investigator reporting the event and subsequently the Chief Investigator (or designated deputy) adjudicating the event, to reach a decision on the expectedness of an event. The reporting investigator and the Chief Investigator (or designated deputy) will be clinicians with substantial experience in treating preterm infants.

Suspected Unexpected Serious Adverse Reactions (SUSARS)

A SUSAR is an Adverse Reaction that is classed as serious, is suspected to be caused by the intervention and is *unexpected* i.e. not consistent with the information about the intervention. SUSARs are subject to expedited reporting. As both feeding regimens are in routine use it is not expected that an unexpected adverse reaction suspected to be caused by one of the feeding regimens is likely to occur.

Trial Steering Committee

A Trial Steering Committee (TSC) will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the lead investigators, an independent chair, two additional independent members and a user representative. The TSC will convene before the start of the trial, every 3 months thereafter or as required throughout the course of the trial. The principal investigator will provide the Human Research Ethics Committee with interim safety reports which arise from the trial steering committee meetings.

Ethics

Ethics approval will be obtained from the Faculty of Health Sciences Human Research Ethics Committee (FHS HREC).

Reporting of results

The results of the study will be included in the MPhil of the principal investigator. Results will also be reported as a journal article for publication in a peer-reviewed journal.

The full protocol

Rapid versus slow advancement of feeds for enterally fed extremely low birth weight infants ≤ 1000 g: a randomised controlled trial

Purpose of the study

The aim of the study is to establish the safety and efficacy of commencing milk feeds at 24 ml/kg/day on the day of birth and advancing enteral feeds at 36 ml/kg/day, in infants with a birth weight ≤ 1000 g. A randomised controlled trial will be conducted using a 2×2 factorial design to assess the higher starting feed volume and faster advancement as separate components.

Background

The optimal enteral feeding regimen has not been established in preterm infants, especially those weighing less than 1000 g birth weight.[1] This is because uncertainty exists regarding when to initiate feeds and how fast feeds should be advanced. The uncertainty is based on studies which raised concerns that early and rapid feeding strategies may be involved in the pathogenesis of necrotising enterocolitis (NEC) [2-4] although causality has not been proven [2-5] and also increase the risk of feed intolerance.

Historically enteral nutrition has been delayed and then followed by slow advancement in increments of between 10 to 24 ml/kg/day. Delayed establishment of full enteral nutrition may lead to suboptimal growth[6] and has been associated with neurodevelopmental delay at 18–22 months.[7]Additionally, infants on slow advancement strategies require nutritional support with parenteral nutrition (PN). This practice requires the insertion of a central line, which increases the risk of infection, health services resource utilisation, and hence the cost of care. Prolonged use of PN is associated with infectious and metabolic risks that have adverse consequences on survival, growth and development.[14]

In 2008, a Cochrane review considered the effect of slow rate advancement of feed on the incidence of NEC.[13] Three randomised trials were included totalling 396 infants. [8-10] The meta-analysis did not show a statistically significant reduction on the risk for NEC. Infants who had slow advancement of feed regained their birth weight later and took longer to establish full enteral feeds.

Early trophic feeding was developed as an alternative to complete enteral fasting for very low birth weight infants during the early neonatal period. Trophic feeding (also known as "minimal enteral nutrition", "gut priming" and "hypocaloric feeding") is conventionally defined as giving small volumes of milk (typically 12–24 ml/kg/day every 1–3 hours) intragastrically starting within the first few days after birth without advancing the feed volumes during the first week postnatally. [15] The Cochrane review did not find any evidence that trophic feeds affected feed intolerance, growth rates or increased the risk for NEC.

Delaying introduction of feeds was then thought to prevent NEC. A Cochrane review of three small trials to determine the effect of delaying introduction of feeds to prevent NEC did not provide evidence to show that it affected the incidence of NEC. [16]

NEC is a serious disease with a high mortality and considerable morbidity that is frequently life-long. Prematurity is the single biggest risk factor for the development of NEC. The mean incidence of NEC in the United States and Canada is about 7% amongst infants with a birth weight between 500 and 1500 g.[21- 24] The estimated rate of death ranges between 20 and 30%, with the highest rate among infants requiring surgery.[25, 26]The total annual estimated cost of caring for infants with NEC in the United States is between $500 million and $1 billion.[25] The pathophysiology of NEC is not well understood and many studies suggest a multifactorial cause.

The slow feeding strategy has now been challenged. Randomized control trials as well as the Cochrane meta-analysis thus far suggests that rapid advancement of feeds in increments of between 30–35 ml/kg/day is safe with no increase in risk for NEC.[1,8-12] The advantages of rapid advancement feeding strategies would improve growth and nutrition, potentially reduce infection rates as few neonates would require PN, fewer intravenous lines would be inserted and potentially shorten hospital stay and reduce costs associated with infection and prolonged hospital stays.

These randomised control trials do have shortfalls. Firstly, in total 496 infants were enrolled in all 4 studies. Only Rayyis et al. enrolled infants < 1000 g, 76 ELBW infants were enrolled and in total only 33 infants less than a 1000 g were randomised to fast advancement group.

Secondly, the sample sizes of all the studies were reasonable small, Rayyis et al. 185 infants is still the biggest study to date. Thirdly, human breast milk was not the primary feeding choice. Rayyis et al. excluded infants who were breastfed and only a third of infants in Caple et al. study received human breast milk. Lastly, feeds were not initiated on day one of life.

Maternal milk is protective against NEC.[17, 18] A small inadequately powered study by Schanler et al. suggested that fortified breast milk might also be protective and showed lower rates of late onset sepsis and earlier discharge when compared to preterm infants receiving formula feeds. [19]A Cochrane review comparing formula fed versus donor breast milk fed infants found a higher rate of short term growth but also a higher risk of developing NEC in the formula fed group. The efficacy of human donor milk in comparison to fresh maternal milk is uncertain.

3 Methods

3.1 Location

The study will be conducted in the tertiary level, neonatal unit at Groote Schuur Hospital in Cape Town, South Africa.

3.2 Design

A 2×2 factorial, randomised controlled trial will be utilised. This design allows both elements of the intervention to be tested separately.

3.3 Hypothesis

Infants ≤ 1000 g at the study site currently have their feeds initiated on the day of birth at 4 ml/kg/day and are advanced at 24 ml/kg/day until they reach full enteral feeds at a volume of 150 ml/kg/day, thereafter the feeds are increased until a volume of 200 ml/kg/day is reached. This usually takes +/- 10 days. Additionally these infants also receive breast milk fortifier (BMF), multivitamins, 5% sodium chloride, phosphate sandoz and iron supplementation as described in 3.10. The study aims to show that the intervention of initiating feeds at a higher volume of 24 ml/kg/day then advancing the feeds at 36 ml/kg/day, results in; better growth patterns as demonstrated by the time to attain a weight of 1500 g and the serial length and head circumference measurements; take fewer days to achieve full enteral feeds; require fewer or no days of PN; and a potentially shorter hospital stay. The study also explores the hypothesis that fast feeding strategies will not increase the background incidence of NEC or mortality.

3.4 Outcomes

3.4.1 Primary outcome

Time to attain a weight of 1500 g

3.4.2 Secondary outcomes

Clinical

Time to regain birth weight, time to discharge, mortality before discharge, number of feed interruptions, NEC, growth in head circumference from birth to discharge, growth in length from birth to discharge and the need for PN.

There are 4 main outcomes of interest are

(i) Time to attain a weight of 1500 g

(ii) Time to discharge

(iii) NEC

(iv)Mortality

Outcomes (i) and (ii) will be compared using hazard ratios. The table below shows the range of hazard ratios (HR) detectable with 80–90% power for a total sample size N (with N/4 in each of the 4 groups) and overall mortality rate based on baseline data from Groote Schuur (35%), and utilising a Cox regression analysis, assuming overall mortality rates of 20–40%, a significance level of 5%, equal size groups and a 10% drop out rate.

Overall mortality rate	**Number**	**HR at 80% power**	**HR at 90% power**
20%	100	1.94	2.15
20%	200	1.60	1.72
30%	100	2.03	2.26
30%	200	1.65	1.78
40%	100	2.14	2.42
40%	200	1.71	1.87

The hazard function can be thought of as an instantaneous probability of having the event in question, and the hazard ratio is interpreted as follows: a hazard ratio of 2 means that; for infants who have not yet died, dropped out or reached the target weight; an infant in the rapid advancement group will be twice as likely to reach the target weight as an infant in the slow advancement group at any instant in time.

All dropouts are assumed to occur towards the beginning of the study, so participants do not contribute to follow up time, resulting in a conservative sample size. Dropout is assumed to be unrelated to the outcome, i.e. uninformative censoring.

Deaths before attaining 1500 g will be treated as censored observations. As a significant difference in mortality is unlikely with this sample size, mortality has been assumed to be the same in both groups for simplicity of sample size calculation, resulting in a conservative estimate of the hazard ratio detectable. Detectable differences in proportions for the binary outcomes of mortality and NEC are shown below, based on baseline rates of 1% for NEC and 30% for mortality.

Overall mortality rate	**Number**	**HR at 80% power**	**HR at 90% power**
20%	100	1.94	2.15
20%	200	1.60	1.72
30%	100	2.03	2.26
30%	200	1.65	1.78
40%	100	2.14	2.42
40%	200	1.71	1.87

3.5 Eligibility

Infants weighing ≤ 1000 g at birth will be eligible for trial entry.

3.6 Exclusions

Infants will be excluded from the study if any of the following are present:

1. Any congenital abnormalities which precludes enteral feeding and is immediately life threatening.
2. Any outborn infants.

3.7 Recruitment and randomisation

On admission, the recruiting clinician will invite informed written consent from parents of eligible infants for participation in the study. Following consent, the clinician will contact the randomisation service and obtain treatment assignment, which will be to one of four groups:
Low volume initiation and slow advancement;
Low volume initiation and rapid advancement;
High volume initiation and slow advancement;
High volume initiation and rapid advancement.

Randomisation will be performed using a computer-generated random group allocation and be administered by telephone by an investigator, who is off site and blinded to the infants' clinical details at study entry. Randomisation will be performed according to gender and weight stratification into two groups: < 700 g and 701–999 g.

3.8 Study duration

Infants will continue in the study up until discharge from hospital.

3.9 Trial feeding schedules

3.9.1 Low volume initiation

Feeding will be initiated on the day of birth with 4 ml/kg/day of expressed human breast milk (EBM) or pasteurised expressed donor human breast milk (DEBM).

3.9.2 High volume initiation

Feeding will be initiated on the day of birth with 24 ml/kg/day of EBM/DEBM.

3.9.3 Slow advancement

On day two after birth the infant will receive 12 ml/kg/day of EBM/DEBM. Thereafter the feeds will be increased in increments of 24 ml/kg/day until enteral feeds of 200 ml/kg/day are attained. If the infant is randomised to the high initiation and slow advancement arm; feeding will be initiated on the day of birth with 24 ml/kg/day of EBM/DEBM, on day two after birth the infant will receive 24 ml/kg/day. Thereafter the feeds will be increased in increments of 24 ml/kg/day until enteral feeds of 200 ml/kg/day are attained.

3.9.4 Rapid advancement

The enteral feeds will be increased in increments of 36 ml/kg/day until enteral feeds of 200 ml/kg/day are attained.

3.10 Standard management

The standard of care during the trial will not differ from current practices at the study site.

All infants will receive continuous nasogastric tube feeds. The nasogastric tube will be changed weekly. The administration set will be changed on a Monday, Wednesday and a Friday. The syringe containing the feed will be changed every 4 hours. Breast milk fortifier (BMF) [FM85® Nestle nutrition] will be commenced 24 hours after enteral feeds are achieved at a volume of 150 ml/kg/day. The BMF dose is 1 g for every 20ml of breast milk. Once a weight of 1200 g is achieved the infant will be switched to 2–hourly bolus feeds. Parenteral nutrition will not form part of the feeding strategy; however it will be initiated for confirmed prolonged feeding intolerance > 3 days and for confirmed cases of NEC.

Only infants < 1200 g qualify for donated human breast milk according to the study site's current guidelines. A preterm formula, Similac Special Care 20® [Abbott Nutrition] is currently used as a substitute feed when breast milk (EBM or DEBM) is not available. For the study period the current DEBM guideline will be adhered to and Similac Special Care 20® will be used as a substitute feed. Therefore formula (Similac Special Care20®) will only be used in the absence of mother's breast milk or donor human breast milk, or the infant's weight exceeds 1200 g and no mother's breast milk is available. All infants will receive supplemental intravenous fluids until full enteral intake is reached. All infants will receive maintenance caffeine at 5 mg/kg/day, nevirapine 2 mg/kg/day (in cases of exposure to maternal human immunodeficiency virus). Daily oral doses of multivitamins (Kiddy-Vits®, Barra Pharmaceutical industries) starting at 0.3 ml and 5% sodium chloride 0.5 ml 8–hourly will be added once enteral feeds of 150 ml/kg/day are achieved and BMF has been commenced. Iron supplementation of 0.2 ml daily dose (containing 6 mg/kg/day elemental iron) will be commenced on day 21 of life. Infants born less than 32 weeks gestation will have phosphate supplementation empirically commenced at 0.5 mmol/kg/day once full feeds are attained at a volume of 150 ml/kg/day and BMF has been commenced. The phosphate dose will be titrated according to the phosphate levels.

In infants where feeds are discontinued and where a subsequent abdominal examination is normal within a 24 hour period, feeds will be recommenced at the volume they were at before ordered NPO and will be subsequently advanced according to their group assignment.

Criteria for NPO:

1) Tense abdominal distension

2) Erythema of the abdominal wall

3) Decreased bowel sounds

4) Gross or occult blood in the stools

5) Abdominal tenderness

6) Bile stained nasogastric aspirate

7) Pneumatosis intestinalis on abdominal Xray

8) Vomits after two consecutive feeds despite normal position of the intragastric tube

An abdominal examination will be deemed normal if the following are absent:

1) Tense abdominal distension

2) Erythema of the abdominal wall

3) Decreased bowel sounds

4) Gross or occult blood in the stools

5) Abdominal tenderness

6) Heavy bile stained nasogastic aspirate

7) Pneumatosis intestinalis on abdominal Xray.

Infants will have daily weights, lengths and head circumferences done weekly and plotted on the Fenton growth charts.

The caloric and protein intake will be calculated daily on all infants for the first 7 days of life.

3.11 Sample size estimate

The sample size for the 2×2 factorial trials is decided by calculating the number needed for each of the main effects, and choosing the largest.[27]This is under the assumption of no interaction between the interventions. If this is not the case a much larger sample is needed (e.g. a four-fold increase to detect an interaction the same size as the main effects. [28] The minimum detectable differences have been calculated for a range of parameters.

3.12 Analysis plan

Data will be checked for missing data and potential erroneous entries will be identified using range checks. Population characteristics for the groups will be described. For each of the time-to-event outcomes (attainment of 1500 g weight, re-attainment of birth weight, death and length of stay), Kaplan-Meier survival curves will be used to illustrate the experience of each treatment group (low volume initiation vs high volume initiation, and slow advancement vs rapid advancement).

It is likely that the hazard of these outcomes changes over time, therefore Wald tests within a Cox regression model with both treatments as covariates will be used to test differences in the hazard between groups, with significance set at $p = 0.05$. The potential interaction between interventions (i.e. the effect of rapid advancement differs between the low and high volume initiation groups) will be tested by including both treatments and an interaction term in the model. However there will only be power to detect an interaction twice the size of the main effects, unless the sample size is increased.

Mortality will be treated as non-informative censoring for weight attainment outcomes. Transfers out of hospital and study drop outs will be treated as censoring, though these are anticipated to be small. Nelson-Aalen plots will be used to assess whether the proportional hazards assumption is reasonable.

Timing of onset of NEC is difficult to determine precisely, therefore NEC will be analysed as a binary outcome. The difference in proportion of babies with NEC will be presented as a relative risk and tested using the chi-squared test. For continuous outcomes, the mean difference between groups will tested with Student's t-test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables.

Analysis will be on an intention to treat basis.

3.13 Trial observations and data collection

Trial data will be captured on a paper Case Record Form.

4 Safety monitoring

4.1 Adverse Reactions (AR)

An adverse reaction (AR) is defined as any untoward or unintended response related to trial intervention. Adverse reactions will be recorded. In the event that an AR is reported during the trial, investigators will assess the severity of the adverse event using the following criteria, detailed on the adverse event case report form (CRF).

- Mild: Awareness of signs or symptoms; but easily tolerated; of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication.
- Moderate: Discomfort severe enough to cause interference with usual infant activities.
- Severe: Inability to carry out usual infant activities; signs and symptoms may be of systemic nature or require medical evaluation and/or treatment.

No further neonates will be enrolled into an intervention arm if it is deemed to be unsafe.

4.2 Specific Adverse Events

Both feeding regimens are used in current clinical practice.

The following specific adverse events will be recorded:

- Episodes of feeds being stopped due to feed intolerance based on pre-defined criteria
- Culture positive sepsis (based on pre-defined criteria) while on parenteral nutrition
- Necrotising enterocolitis based on pre-defined criteria
- Complications relating to percutaneous catheters

4.3 Serious Adverse Events/Reactions

All serious adverse reactions will be reported to the trial co-ordinator. Serious adverse events (SAE) or reactions can be defined as any untoward medical occurrence or effect that:

- results in death
- is life-threatening
- prolongs hospitalisation
- results in persistent or significant disability or incapacity

4.4 Expected SAEs/clinical outcomes due to preterm birth

There are multiple serious complications that could occur as a consequence of preterm birth. It will be at the judgement of the investigator reporting the event and subsequently the Chief Investigator (or designated deputy) adjudicating the event, to reach a decision on the expectedness of an event. The reporting investigator and the Chief Investigator (or designated deputy) will be clinicians with substantial experience in treating preterm infants.

4.5 Suspected Unexpected Serious Adverse Reactions (SUSARS)

A SUSAR is an Adverse Reaction that is classed as serious, is suspected to be caused by the intervention and is unexpected i.e. not consistent with the information about the intervention. SUSARs are subject to expedited reporting. As both feeding regimens are in routine use it is not expected that an unexpected adverse reaction suspected to be caused by one of the feeding regimens is likely to occur.

5 Trial sponsor and oversight committees

5.1 Trial Sponsor

No Sponsor.

5.2 Trial Steering Committee

A Trial Steering Committee (TSC) will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the lead investigators, an independent chair, two additional independent members and a user representative. The TSC will convene before the start of the trial, every 3 months thereafter or as required throughout the course of the trial. The principal investigator will provide the Human Research Ethics Committee with interim safety reports which arise from the trial steering committee meetings.

6 Feasibility

The neonatal unit at Groote Schuur Hospital has 150–200 of infants with birth weights < 1000 g at birth per year.

7 Funding

I have no funding for the study.

8 Regulatory approvals

8.1 Institutional approval

The study will be submitted to the departmental research committee (DRC).

8.2 Research ethics approval

Following DRC approval the study protocol will be submitted to the Human Research Ethics Committee (HREC) at the University of Cape Town.

9 Appendices

9.1 Case Record form

9.2 Parental information

9.3 Parent consent form

9.4 Fenton Growth Chart

9.5 SAE and SUSAR reporting form

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Part B: Structured Literature Review

Structured Literature Review

Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants

Abstract

Background

The optimal enteral feeding regimen for preterm infants has not been established, and remains particularly challenging in infants weighing less than 1000 g. The need for early nutrition and optimal growth and the debate on the most appropriate feeding strategy is nuanced by studies suggesting that early and rapid feeding strategies may increase the risk of feeding intolerance and may be involved in the pathogenesis of necrotising enterocolitis (NEC).

Objectives

To examine the effect that the rate of advancement of enteral feeds has on the incidence of NEC, mortality, growth, health care utilisation and other morbidities in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants.

Methods

The Cochrane database was searched and Medline was searched using Pubmed (www.ncbi.nlm.nih.gov). We searched for randomised or quasi-randomised controlled trials assessing the effect of slow (up to 20 ml/kg/day) versus faster rates of enteral feed volume advancement on the incidence of NEC in enterally fed infants who were < 32 weeks gestation or < 1500 g at birth.

Results

Five randomised controlled trials were identified, in which 585 infants were recruited. Only 62/585 (10.6%) of the infants recruited weighed < 1000 g.
The trials defined slow advancement rates as daily increments of between 15–20 ml/kg/day and fast advancement rates as 30–35 ml/kg/day. None of the trials showed a statistically significant effect of feeding strategy on the risk of NEC or mortality. All five trials demonstrated that infants randomised to the slow advancement group took statistically

significantly longer to establish full enteral feeds and to regain their birth weight, but none of these trials assessed neurodevelopmental outcomes. There was a wide variation in the extent of breast milk use and the range of birth weights included in each trial.

Conclusion

The volumes at which feeds are advanced have often been suggested as playing a role in the pathogenesis of NEC. This review suggests that decreasing the advancing enteral feed volume does not reduce the risk of NEC, but the data are limited by small numbers and wide variation in feed types and birth weights. Moreover, the long-term effect of establishing enteral feeds sooner and regaining birth weight faster in the fast advancement group is unknown. No inferences can be made in the subgroup of high risk infants < 1000 g, due to the limited numbers in this category. Further randomised controlled trials are needed to provide high quality evidence to inform the correct approach to feeding preterm infants, particularly ELBW infants.

Background

The timeous achievement of full enteral nutrition in a preterm infant is a critical prerequisite for optimal growth, neurodevelopment and long-term wellbeing. The optimal enteral feeding regimen for preterm infants has not been established, and remains particularly challenging in infants weighing less than 1000 g at birth.[1] The debate on when to initiate feeds and the most appropriate speed of advancement of feed volumes is nuanced by studies raising concerns that early and rapid feeding strategies increase the risk of feeding intolerance; such a strategy may be involved in the pathogenesis of necrotising enterocolitis (NEC),[2-4] although causality has not been proven.[2,4,5] A recent international survey by Klingenberg et al. highlights a wide variation in enteral feeding practices among clinicians – emphasizing the need for evidence-based data in this area.[6]

The recognised association between NEC and enteral feeding, suggests that feeding strategy is a potentially modifiable risk factor.[7, 8] Historically, enteral nutrition has been delayed for one or several days and milk feeds are then introduced with slow incremental advancement of 10–20 ml/kg/day.[9] However, delayed establishment of full enteral nutrition may lead to suboptimal growth[10] and has been associated with neurodevelopmental delay at 18–22 months. [11] Moreover, infants on slow advancement strategies typically require

nutritional support with parenteral nutrition (PN). This practice frequently requires the insertion of a central line, which increases the risk of infection; health resource utilisation, and the cost of care.[12] Prolonged use of PN is also associated with abnormal metabolism and hepatic toxicity that have adverse consequences on survival, growth and development. [12]

NEC is a serious disease with a high mortality and considerable morbidity that is frequently life-long. Prematurity is the single biggest risk factor for the development of NEC. The mean incidence of NEC in the United States and Canada is 7% amongst infants with a birth weight between 500 and 1500 g.[13-16] The estimated death rate ranges from 20 to 30%, with the highest rate among infants requiring surgery.[17,18] The total annual estimated cost of caring for infants with NEC in the United States is between $500 million and $1 billion.[17] Developing countries have a high rate of premature deliveries, however paucity of data exists regarding the long-term outcomes of NEC in this setting.[19]

Objectives

The primary objective was to examine the effect that the rate of advancement of enteral feeds has on the incidence of NEC. The secondary objective was to examine the effect that the rate of advancement of enteral feeds has on mortality before discharge, growth, health resource utilisation and other morbidities in very low birth weight (VLBW) and extremely low birth weight (ELBW) infants.

Methods

A structured literature search was done using the Cochrane database and using Pubmed (www.ncbi.nlm.nih.gov) to search Medline. The search was conducted on the 1st of March 2013 and no year limit or language restrictions were set for the search. A PICO (Population, Intervention, Comparator and Outcome) framework was used to develop inclusion and exclusion criteria for study selection for the primary objective. We used a combination of the following text words and MeSH terms: preterm feeding, infant feeding, infant nutrition, preterm nutrition and feed advancement.

The titles and abstracts of the articles were retrieved based on the PICO framework. Letters, comments, guidelines and review articles were excluded. Full texts of the articles defined by the inclusion and exclusion criteria were reviewed. References of these articles were retrieved and scrutinised for further relevant trials.

Only randomised or quasi randomised controlled trials of enterally fed preterm infants < 32 weeks gestation or < 1500 g at birth, that assessed the effect of slow (up to 20 ml/kg/day) versus faster rates of enteral feed volume advancement on the incidence of NEC in the study participants were included.

Results

The online database search was done on the 1st March 2013. After reviewing all the titles and abstracts, eight randomised controlled trials were identified that could potentially fit criteria for inclusion. These were reviewed in full text after which five randomised controlled studies are included in this literature review. The study sites were neonatal units in North America [20, 21], India [9, 22] and Turkey [23]. The summarised descriptive data from the five included trials are shown in Table 1. One randomised controlled trial by Sergeyev, [24] was excluded as the study compared feed advancement according to a standardised feeding scheduled versus individualised feed volume advancement. The study did not compare the effect of slow (up to 20 ml/kg/day) versus faster rates of enteral feed volume advancement. Two further trials were also excluded on the basis that the both randomised groups were considered to be receiving slow advancement of enteral feeding volumes. In the first of these two trials, Book et al. conducted a randomised controlled trial comparing enteral feeding volume advancements of 10 ml/kg/day versus 20 ml/kg/day.[5] In the second of these two trials, Berseth et al. randomised 141 preterm infants to one of two feeding schedules; one group was fed 20 ml/kg/day daily for the first 10 days, the other was fed 20 ml/kg/day on the first day and thereafter feed volume was increased daily by 20 ml/kg/day until 140 ml/kg/day was achieved and this volume was maintained until the tenth day of life. [3] The excluded trials are summarised in Table 2.

The data of the included were collected between 1999 and 2012. All trials specified birth weight eligibility criteria but the actual birth weight criteria varied between trials. A total of 585 infants were included in the studies, of which 293 (50%) were randomised to the fast advancement group. Only 105/585 (17.9%) of the participants weighed < 1000g; Rayyis et al.[20] included 76 ELBW infants and Kargol et al.[23] included 29 ELBW infants. Thirty-three of the ELBW infants in Rayyis et al.[20] were randomised to the fast advancement group; it is not documented how many ELBW infants were randomised to the fast advancement group in the study by Kargol.[23] The sample sizes varied from 53 to 185 participants.

All five trials initiated intragastric bolus feeds within the first five days of life. The infants were randomised to one of two feeding advancement schedules; slow (15–20 ml/kg/day) versus fast (30–35 ml/kg/day).

The use of breast milk was not the same in all trials. All the infants recruited by Salhorta et al. received expressed mothers breast milk,[9]whereas Rayyis et al. excluded infants receiving breast milk.[20] The remaining trials fed infants a combination of breast milk and formula. Only two studies make mention of whether routine PN formed part of the feeding schedule; Kargol et al. used PN[23] whereas participants in Krishnamurthy's trial did not receive routine PN because of resource constraints; facilities for proper preparation, mixing and administration of PN was not available in this setting.[22]

All five trials had specific criteria and definitions which mandated a feed interruption or keeping the infant nil per mouth (NPO). Although varied, the common criteria were the detection of gastric aspirates/residuals (the volume of the gastric content aspirated prior to the planned gastric feed) and abdominal distension. The trials also clearly stipulated the manner in which feeds should be commenced following a period of NPO. The criterion for a mandated feed interruption is reported in Table 3.

The quality of the included trials is described in Table 4. Randomisation methods to ensure allocation concealment were acceptable in all trials – the methods used included random number sequence generation or computer generated sequence, blinded drawing of envelopes by clinicians not involved in the trials or opaque envelopes. Blinding of the intervention to the clinicians was not possible due to the nature of the intervention. A clinical suspicion of NEC was categorized according to the Bell stages in all the trials.[25] Bell stage II includes radiographic findings of pneumatosis intestinalis or portal vein gas with clinical signs including poor feeding, increased gastric residuals, or abdominal distension with bloody stools. Bell stage III includes radiographic observation of pneumoperitoneum with the previously described clinical signs associated with deterioration of vital signs and septic shock. Only infants with signs consistent with Bell stage II or III were included in the NEC outcome of the trials.

Blinding of the clinicians reviewing the abdominal radiographs to the allocation group was only performed in three of the five trials.[20-22] Overall the trials were of good methodological quality with no obvious selection bias or attrition bias.

Outcomes

All the trials reported on the incidence of NEC. Other outcomes included time to regain birth weight, mortality to discharge, time to establish full enteral feeding, duration of hospital stay, feeding intolerance and rates of late onset sepsis. None of the five studies assessed neurodevelopmental outcomes.

The incidence of NEC in all five trials is reported in Table 5. None of the trials detected a statistically significant effect on the risk of NEC.

Mortality in the four trials that reported this outcome is shown in Table 5. None of the trials reported a statistically significant effect of feeding strategy on the risk of death. Caple did not report on mortality.[21]

All five studies demonstrated that it took statistically significantly longer to regain birth weight in those infants randomised to the slow advancement group. These data are shown in Table 7. Infants in the slow advancement group regained their birth weights 2 to 6 days later than those in the faster advancement groups. Long-term growth parameters were not reported in any of the trials.

All five studies demonstrated that it took statistically significantly longer to establish full enteral feeds in those infants randomised to the slow advancement group. These data are shown in Table 8. Infants in the slow group established full enteral feeds 2–5 days later than those infants in the faster advancement groups.

Only three studies reported on the incidence of feeding intolerance. These data are shown in Table 9. Feeding intolerance was common in both groups. None of the studies reported a statistically significant difference between the two feeding strategies.

Only Krishnamurthy et al. and Kargol et al. reported on the incidence of late onset sepsis.[22, 23] These data are shown in Table 10. Only one study reported a significant difference between the groups: Kargol et al. found less late onset sepsis in the rapid feeding advancement group.[23]

The duration of hospital stay was reported in four trials. These data are shown in Table 11. Rayyis et al.[20] and Caple et al.[21] did not report a statistically significant difference between the two groups. Krishnamurthy et al.[22] and Kargol et al.[23] however reported a statistically significantly longer duration of stay in the slow advancement group.

Discussion

Each of the five randomised controlled trials suggest that the practice of low volume increment feed advancement of ≤ 20 ml/kg/day does not reduce the risk for developing NEC compared to incremental volumes of up to 35 ml/kg/day.

Advancing the feeds at a slow rate resulted in a statistically significant delay in the time taken to regain birth weight and to establish full enteral feeds. Infants randomised to the slow advancement group regained their birth weight 2–6 days later and established full enteral feeds 2–5 days later. The clinical significance of this effect is unknown as the long-term effect on survival and/or neurological outcome was not reported in any of the five trials reviewed. The short-term effect of the improved early weight gain is also unknown, as the effect on the duration of hospital in the included trials detected varied outcomes.

Despite the above findings, these data cannot reliably inform practice because of several important limitations in the included trials. The sample sizes are relatively small, the use of breast milk and the birth weight of included infants were very variable between trials and none of the trials were sufficiently powered to detect clinically or statistically significant differences in the proportion of infants with NEC. Moreover, NEC was defined with very restrictive criteria, which may have inappropriately excluded a large number of infants. The majority of the trials included infants being fed with formula or formula and breast milk. Only the small trial of Salhorta et al.[9] used breast milk as the primary feed during the study, while Rayyis et al.[20] excluded infants who were receiving breast milk. A Cochrane review by Quigley et al. demonstrated that formula feeds increased the risk for NEC.[26] The feeding strategies in high risk infants may have to differ between breastfed and formula fed infants. Data from the Loire Infant Follow-up Team (LIFT) and EPIPAGE cohorts suggest that infants who are breastfeeding at the time of discharge were observed to have better neurodevelopmental outcomes in spite of suboptimal initial weight gain.[27]

There is a paucity of data delineating the effect and outcomes of rapid advancement of feeds in ELBW and intrauterine growth restricted infants. Only a limited number of infants with a

birth weight of < 1000 g (10.6%) were included in these trials. The trials tended to exclude infants with severe respiratory distress, infants on ventilatory and or inotropic support, infants with these morbidities are at high risk for NEC; the generalisability of the findings of the trials is particularly limited in this context.

Slow advancement of enteral feeds results in delayed establishment of enteral feeds. Faster advancement increments may result in more feed interruptions, delayed establishment of full feeds, increased use of PN and increased late-onset sepsis, however the trials did not report increased rates of feeding intolerance and the consequences of prolonged PN use, and incidence of late-onset sepsis is still unknown.

The incidence of NEC has remained unchanged during the past 20 years, presumably because improvements in neonatal intensive care have resulted in improved early neonatal survival rates, particularly in ELBW infants.[28] Many infants who develop NEC have received enteral feeds and the early introduction and rapid advancement of enteral feeds have previously been implicated in the pathogenesis of NEC.[7,8] The timing, volume of the initiation as well as the rate of advancement of enteral feeds may collectively or independently have the potential to determine important outcomes such as the risk for NEC, late-onset sepsis and long-term neurodevelopment outcomes.[28] The trials reviewed only compared slow advancement of enteral feeds versus faster rates of advancement and did not examine volume of initiation of feeds and the outcomes thereof. In a Cochrane review, Bombell et al. did not find any evidence that trophic feeds affected feed tolerance, growth rates or the risk for NEC.[29] In a separate Cochrane review, delaying the introduction of feeds did not prevent NEC.[30] Leaf et al. also demonstrated in a subgroup of growth restricted infants that commencement of enteral feeds “early” (by the second day after birth) compared to “late” (by the sixth day after birth) resulted in earlier achievement of full enteral feeds and did not appear to increase the risk for NEC.[31]

This review and a recent international survey by Klingenberg et al. highlighting a wide variation in enteral feeding practices among clinicians[6] – emphasises the need for further randomised controlled trials to provide high quality evidence to inform the correct approach to feeding preterm infants. These trials should aim to examine both elements of feeding, namely the initiating volume as well as the advancement rate. These trials must aim to recruit the high risk groups for NEC; ELBW infants, intrauterine growth restricted infants and ventilated infants and long term follow-up describing late mortality and neurodevelopmental

morbidity should be included. Breastfed infants should be included and analysis should include stratification according to predominant feed type. It is important that these trials be sufficiently powered to assess important outcomes such as the incidence of late-onset sepsis and the utilisation of PN.

Table 1: Summary of included trials

Author, year	Sample size	< 1000 g	Inclusion criteria	Intervention	Feed types	Age at starting feeds (days)	Routine PN
Rayyis 1999	185	76 (41%)	< 1500 g	Feeds advanced at 15 ml/kg/d (n=98) vs 35 ml/kg/d (n=87)	Only formula	Slow 5 (3–7) Fast 4 (3–7)	Not documented
Caple 2004	155	0	1000–2000 g (appropriate birth weight for GA and GA< 35weeks	Feeds advanced at 20 ml/kg/d (n=72) vs 30 ml/kg/d (n=83)	EBM or formula or a combination of both	Slow 2.6 (0–16) Fast 2.2 (0–20)	Not documented
Salhorta 2004	53	0	< 1250 g	Feeds advanced at 15 ml/kg/d (n=26) vs 30 ml/kg/d (n=27)	EBM only	Trophic at 5 ml/kg/d 4 hrly for 1st 48 hours, then randomised	Not documented
Krishnamurthy 2010	100	0	Infants < 34 weeks with weight 1000–1500 g	Feeds advanced at 20 ml/kg/d (n=50) vs 30 ml/kg/d (n=50)	EBM or formula or a combination of both	Initiated within 1st 24 hours	No
Kargol 2012	92	29 (32%)	Infants < 32 weeks with weight 750–1250 g	Feeds advanced at 20 ml/kg/d (n=46) vs 30 ml/kg/d (n=46)	EBM or formula or a combination of both	Trophic started at 24–48hrs, maintained for 5–6 days, then advanced slow or fast	Yes

Table 2: Summary of excluded trials

Author, year	Intervention
Book 1976	Feeds advanced at 10 ml/kg/day vs 20 ml/kg/day
Berseth 2003	One group fed 20 ml/kg/day for 1st 10 days vs 20 ml/kg /day on the first day and increased by 20 ml/kg/day until a volume of 140 ml/kg/day was achieved
Sergeyev 2010	compared feed advancement according to a standardised feeding scheduled versus individualised feed volume advancement.

Table 3: Criteria for feed interruptions

Author , Year	Criteria
Rayyis 1999	Milk feeds were stopped if any of the following occurred; residual gastric contents constituted > 30% of the previous feed volume, or if there was abdominal distension or tenderness, or bloody stools (including occult blood)
Caple 2004	Milk feeds were stopped if any of the following occurred; residual gastric contents constituted more than one third of the previous feed volume, or if there was frequent vomiting, or if there was abdominal distension, or bloody stools (including occult blood)
Salhorta 2004	Milk feeds were stopped if the residual gastric content constituted > 30% of the previous feed volume or abdominal distension
Krishnamurthy 2010	Milk feeds were stopped if any of the following occurred; residual gastric contents constituted > 50% of the previous feed volume (feeds were delayed if the residual volume was between 25 and 50%, or > 3 episodes of apnoea in the preceding hour, or abdominal distension or tenderness, or bloody stools (including occult blood)
Kargol 2012	Milk feeds were stopped if any of the following occurred; residual gastric contents constituted > 50% of the previous feed volume or > 5 ml/kg ,or vomiting > 3 times in 24 hours, or increase in abdominal girth > 2 cm between feeds, or abdominal tenderness or erythema, or bloody stools, or reduced bowel sounds , or recurrent apnoea

Table 4: Quality of the included trials

	Rayyis 1999	**Caple 2004**	**Salhorta 2004**	**Krishnamurthy 2010**	**Kargol 2012**
Randomisation methods	Not documented	Random number sequence	Computer generated sequence	Computer generated sequence	Computer generated sequence
Allocation concealment	Opaque sealed envelopes drawn	Envelope drawn blindly by clinicians not involved in the study	Opaque sealed envelopes drawn	Opaque sealed envelopes drawn	Opaque sealed envelopes drawn
Clinical Blinding	Not blinded to intervention after randomisation	Not blinded to intervention after randomisation	Not blinded to intervention after randomisation	Not blinded to intervention after randomisation	Not blinded to intervention after randomisation
X-ray blinding	Interpreted by clinician blinded to study group	Interpreted by clinician blinded to study group	Not documented	Interpreted by clinician blinded to study group	Not documented

Table 5: Incidence of NEC

Author, year	Slow advancement group	Fast advancement group	p-value
Rayyis 1999	13/98	8/87	0.5
Caple 2004	2/83	3/72	0.66
Salhorta 2004	0/26	2/27	Not documented
Krishnamurthy 2010	1/50	2/50	1.0
Kargol 2012	5/46	4/46	0.42

Table 6: Mortality

Author, year	Slow advancement group	Fast advancement group	p- value
Rayyis 1999	2/98	3/87	Not documented
Caple 2004	Not reported	Not reported	Not reported
Salhorta 2004	12/26	7/27	Not documented
Krishnamurthy 2010	6/50	4/50	0.51
Kargol 2012	4/46	3/46	0.62

Table 7: Time to regain birth weight

Author, year	Slow advancement group median time in days, (IQR)	Fast advancement group median time in days, (IQR)	p-value
Rayyis 1999	15 (11-20)	12 (8-15)	0.05
Caple 2004	13 (5-34)	11 (3-26)	<0.01
Salhorta 2004	23 (16-38)	18 (11-30)	Not documented
Krishnamurthy 2010	22 (14-28)	16 (12-23)	<0.001
Kargol 2012	23 (14.2-29.6)	19.2 (12.3-24.6)	0.005

Table 8: Time to establish full enteral feeding

Author, year	Slow advancement group median time in days, (IQR) or mean (±SD)	Fast advancement group median time in days, (IQR) or mean (±SD)	p-value
Rayyis 1999	15 (12-21)	11 (8-15)	<0.001
Caple 2004	10 (8-27)	7 (5-48)	<0.01
Salhorta 2004	14.8 (+/-1.5)	10 (+/- 1.8)	<0.001
Krishnamurthy 2010	9 (9-11)	7 (7-9.5)	<0.001
Kargol 2012	22.3 (+/- 6.4)	19.1 (+/- 4.3)	0.001

Table 9: Feeding intolerance

Author, year	Slow advancement group	Fast advancement group	p-value
Rayyis 1999	Not reported	Not reported	Not reported
Caple 2004	Not reported	Not reported	Not reported
Salhorta 2004	17/26	14/27	Not documented
Krishnamurthy 2010	12/50	8/50	0.34
Kargol 2012	13/46	11/46	0.44

Table 10: Late onset sepsis

Author, Year	Slow advancement group	Fast advancement group	p-value
Rayyis 1999	Not reported	Not reported	Not reported
Caple 2004	Not reported	Not reported	Not reported
Salhorta 2004	Not reported	Not reported	Not reported
Krishnamurthy 2010	5/50	4/50	Not documented
Kargol 2012	10/46	6/46	0.01

Table 11: Duration of hospital stay

Author, year	Slow advancement group median duration of hospital stay in days, (IQR)	Fast advancement group median duration of hospital stay in days, (IQR)	p-value
Rayyis 1999	47 (31-67)	43 (29-62)	0.3
Caple 2004	31 (12-190)	26 (11-111)	0.15
Salhorta 2004	Not reported	Not reported	Not reported
Krishnamurthy 2010	11 (10-15)	9.5 (8.4-13.8)	0
Kargol 2012	35.1 (17-85)	29.2 (13-71)	0.001

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Part C: Manuscript

Manuscript

High or low enteral feed volume initiation followed by rapid or slow advancement of enteral feeds for extremely low birth weight infants: a randomised controlled trial

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Abstract

Background

Optimal feeding regimens in infants weighing ≤1000g have not been established.

Objective

To establish safety and efficacy of commencing feeds at 24ml/kg/day on the day of birth and advancing feeds at 36ml/kg/day, in infants weighing ≤1000g.

Methods

In this 2x2 factorial randomised controlled trial we assessed initiation enteral volumes and advancement rates as separate components. Infants weighing ≤1000g were randomized to one of four groups each receiving exclusive feeds of human milk: low volume initiation (4 ml/kg/day)/slow advancement (24ml/kg/day); low volume initiation (4ml/kg/day)/rapid advancement (36ml/kg/day); high volume initiation (24 ml/kg/day)/slow advancement (24ml/kg/day); or high volume initiation (24ml/kg/day)/rapid advancement (36ml/kg/day). The primary outcome was the time to attain a weight of 1500g. Cox regression was used for time-to-event outcomes and logistic regression for binary outcomes, with treatment effects presented as hazard ratios and odds ratios respectively.

Results

Two hundred infants were recruited (51 low/slow, 47 low/rapid, 52 high/slow, 50 high/rapid). Infants on rapid advancement were the quickest to reach a weight of 1500g, (hazard 2.3, p=0.003, 95% CI 1.3–4.0). Rapid advancement was associated with fewer days to regain birth weight, (hazard 2.3, p=0.001, 95% CI 1.4–3.6) and fewer days in hospital (hazard 1.9,

p=0.006, 95% CI 1.2–3.1).There were no significant differences in the rates of NEC, feed intolerance, or late-onset sepsis between the groups.

Conclusion

Higher initiation feed volumes and larger daily feed increments in infants ≤1000g birth weight, was well tolerated, increased early weight gain and reduced hospital stay. This feeding practice does not appear to increase the risk for NEC.

Introduction

The debate on when to initiate feeds and the speed of advancement of feed volumes is nuanced by studies raising concerns that early and rapid feeding strategies may be implicated in the pathogenesis of necrotising enterocolitis (NEC), [1-3] however causality remains uncertain.[1, 3, 4] A recent international survey highlights wide variation in enteral feeding practices among clinicians – emphasizing the need for evidence-based data in this area.[5]

Traditionally, a slow advancement feeding strategy has usually been adopted.[6] A delay in attaining full enteral nutrition may lead to suboptimal growth[7] and has been associated with neurodevelopmental delay at 18–22 months.[8]

A rigorous systematic review and meta-analysis of five randomised controlled trials (RCT) including 585 infants, suggests that rapid advancement of feeds in increments of between 30–35 ml/kg/day is safe with no increase in risk for NEC.[6,9-14]

There are several limitations that hinder the application of the findings of the meta-analysis;[13] sample sizes are small and extremely low birth weight (ELBW) infants are not well represented. ELBW infants; 105 of 585, were recruited in only two studies.[9, 12]

Human breast milk was not the primary feeding choice. Rayyis et al.[9] excluded infants who were breastfed and only a third of infants in Caple et al.[10] study received human breast milk.

Within our institute, Lango et al. demonstrated that early introduction of enteral breast milk feeding with minimal use of PN in ELBW infants, resulted in a mean growth velocity comparable with that achieved by infants who received substantial early PN with later establishment of enteral feeds.[15] A more rapid advancement of enteral feeds may further reduce early nutritional deficits and improve growth velocity in ELBW infants.

Our objectives were to examine the outcomes of both the initiating and advancement enteral feed volumes in infants weighing ≤ 1000 g.

Methods

The study was conducted in the tertiary level, neonatal unit at Groote Schuur Hospital in Cape Town, South Africa. Approximately 2000 babies are admitted to this 75-cot unit annually, 10% of infants are ELBW. The study conforms to the principles of the 2008 Declaration of Helsinki [16], and written informed parental consent was obtained. The study was performed between August 2011 and February 2013. The research was approved by the University of Cape Town, Faculty of Health Sciences, Human Research Ethics Committee. The trial is registered with the ISRCTN Register (http://isrctn.org) (identifier ISRCTN96923718).

Design

We used a 2×2 factorial designed RCT. This approach allowed both interventions, the higher starting enteral feed volume and the faster advancement enteral feed volume to be assessed separately. The factorial design also allowed the interactions between the interventions to be examined, though no interaction between the treatment interventions was assumed when calculating sample size.

Outcome measures

The primary outcome was the time to attain a weight of 1500 g. This reflects the weight at which infants in our service become eligible for full-time kangaroo mother care (KMC).

Secondary outcomes were: 1) time to regain birth weight; 2) number of feed interruptions; 3) incidence of NEC; 4) mortality rate before discharge; 5) growth in head circumference from birth to discharge; 6) growth in length from birth to discharge; 7) PN utilisation; 8) incidence of late-onset sepsis; and 9) duration of hospital stay.

Recruitment and randomization

All inborn infants with a birth weight of ≤ 1000 g were eligible for trial entry. All outborn infants were excluded. Infants with any congenital abnormalities; which precluded enteral feeding or were immediately life threatening were also excluded.

Following written informed parental consent, eligible infants were randomly and blindly assigned to one of four groups:

Low volume initiation and slow advancement;
Low volume initiation and rapid advancement;
High volume initiation and slow advancement;
High volume initiation and rapid advancement.

Randomization was performed using a computer-generated random group allocation and was administered by telephone from an investigator, who was off site and blinded to the infant's clinical details at study entry. Thereafter, neither carers nor investigators were blinded to the allocation group. Randomization was performed according to gender and weight stratification into two groups: < 700 g and 701–999 g.

Low volume initiation

Feeds were initiated on the day of birth with 4 ml/kg/day of maternal expressed human breast milk (EBM) or pasteurised donor human expressed breast milk (DEBM).

High volume initiation

Feeds were initiated on the day of birth with 24 ml/kg/day of EBM/DEBM**.**

Slow advancement

On day two after birth the infant received 12 ml/kg/day of EBM/DEBM. Thereafter the feeds were increased in increments of 24 ml/kg/day until enteral feeds of 200 ml/kg/day were attained. If the infant was randomized to the high/slow group; feeds were initiated on the day of birth at 24 ml/kg/day of EBM/DEBM, on day two after birth the infant received 24 ml/kg/day. Thereafter the feeds were increased in increments of 24 ml/kg/day until enteral feeds of 200 ml/kg/day were attained.

Rapid advancement

Feeds were increased in increments of 36 ml/kg/day until enteral feeds of 200 ml/kg/day were attained.

Medical management

All infants received exclusive breast milk (EBM/DEBM), until they weighed 1200 g. All infants received continuous intragastric feeds. Breast milk fortifier (BMF), [FM85® Nestle nutrition], at a concentration of 1 g per 20 ml of breast milk was added after an enteral feeding volume of 150 ml/kg/day was attained. At a weight of 1200 g, the infant was switched to 2–hourly bolus feeds via the intragastric tube. Parenteral nutrition was only initiated when prolonged feeding intolerance of > 3 days occurred and/or for confirmed cases of NEC.

A preterm formula milk, Similac Special Care® 20 [Abbott Nutrition], was used when EBM/DEBM was not available. All infants received supplemental intravenous fluids until a full enteral intake of 150 ml/kg/day was reached. All infants received caffeine 5 mg/kg/day, and in cases of exposure to maternal human immunodeficiency virus, nevirapine 2 mg/kg/day was also given. After enteral feeds of 150 ml/kg/day were achieved and BMF had been commenced, the following supplements were added: 0.3 ml oral multivitamins [kiddy-vit® Barra Pharmaceutical] daily; 0.5 mmol oral sodium chloride 8–hourly; infants, who were ≤ 32 weeks gestation at birth were also given 0.5 mmol/kg/day of oral phosphate – the phosphate dose was titrated according to the phosphate levels. Oral ferrous lactate 0.2 ml daily was added from day 21 of life.

Infants were weighed daily; lengths and head circumferences were measured weekly and these measurements were plotted on the Fenton growth charts.[17]

The indications to discontinue feeds were: tense abdominal distension; erythema of the abdominal wall; decreased bowel sounds; gross or occult blood in the stool; abdominal tenderness; bile stained gastric aspirates; pneumatosis intestinalis; or vomiting after two consecutive feeds despite correct position of the intragastric tube.
Only infants with signs consistent with Bell stage II or III [18] were included in the NEC outcome. Bell stage II includes radiographic findings of pneumatosis intestinalis or portal vein gas with clinical signs including poor feeding, increased gastric residuals, or abdominal distension with bloody stools. Bell stage III includes radiographic observation of pneumoperitoneum with the previously described clinical signs associated with deterioration of vital signs and septic shock.

In infants where feeds were discontinued after presenting with abdominal distension only but subsequently had a normal abdominal examination within 24 hours, their feeds were recommenced at the volume they had previously attained; feeds were subsequently advanced according to their group assignment.

Infants remained on the study until discharge from hospital.

Sample size estimate

We based the sample size calculation on an overall mortality rate of 40% utilising baseline data from Groote Schuur Hospital in infants < 1000 g. Assuming, equally sized groups, a 10% drop out rate, and a significance level of 5%; we estimated that a total sample size of 200 patients would provide 80% power to detect a hazard ratio of 1.7 for the primary outcome of time to attain a weight of 1500 g. No interaction between the treatment interventions was assumed.

Data analysis

The data was analysed with Stata version 12 (Stata Corporation, College Station, USA). All analyses were carried out on an intention to treat basis. Statistical significance was set at $p = 0.05$. For each of the time-to-event outcomes (attainment of 1500 g weight, re-attainment of birth weight and length of stay), Kaplan-Meier survival curves were used to compare treatment groups (low volume initiation vs. high volume initiation, and slow advancement vs. rapid advancement). Cox regression models were used to estimate hazard ratios and associated 95% confidence intervals comparing treatment groups. Plots and tests of Schoenfeld residuals were used to check the proportional hazards assumption. If hazards were non-proportional, the hazards were estimated separately for two intervals, by splitting the data according to the median survival time.[20] Interaction between the interventions (i.e. the effect of low and high volume initiation on outcomes according to speed of advancement) was tested, although the study was underpowered to detect treatment effects in the presence of an interaction. For weight attainment outcomes, patients were censored if they died before attaining the weight. Log rank tests and Cox regressions were stratified by gender and birth weight group as per randomisation strata.

The binary outcomes of NEC, mortality, feed interruptions and the use of PN were analysed using logistic regression, adjusting for gender and birth weight group as per randomisation strata. Differences between treatment groups were presented as odds ratios and associated

confidence intervals. Growth in head circumference and length between birth and discharge was calculated for babies who were discharged home. Data were log-transformed due to skewness before analysis using linear regression, adjusting for gender and birth weight group as per randomisation strata. Differences between treatment groups were presented as the percentage difference and associated confidence intervals.

Results

During the enrolment period, 214 ELBW infants were admitted to the neonatal unit. Two hundred infants were recruited from August 2011 until February 2013. The flow of recruitment, reasons for exclusion and group totals are shown in Figure 1. Baseline demographic and clinical characteristics were similar between the four groups; these data are shown in Table 1.

There were no protocol violations.

Primary outcome: time to attain 1500 g

Figure 2 shows the Kaplan-Meier plot showing the time to attain 1500 g. Results from the Cox regression models for the time to attain 1500 g are shown in Table 2. Examining the interventions separately and assuming proportional hazards, infants receiving rapid advancement were 1.5 times more likely to reach a weight of 1500 g before the infants receiving slow advancement of enteral feeds (hazard 1.48, p = 0.03, 95% CI 1.05–2.09). There was evidence of an interaction between the interventions (p = 0.02).When including the interaction between the interventions, infants on the high volume initiation and rapid advancement feeding schedule were 1.6 times more likely to reach 1500 g earlier than the low volume initiation and slow advancement group. There was evidence that the hazard for the effect of rapid advancement was not constant over time (p = 0.01), therefore the data were split at the median time to attain a weight of 1500 g (47 days); infants in the high and rapid group were more than twice as likely to reach 1500 g compared to the low and slow group before 47 days. The effect was lost after 47 days. There was no evidence of non-proportional hazards after splitting the time period.

Secondary outcomes: growth and age at discharge

Figure 3 shows the Kaplan-Meier plot showing the time to regain birth weight. Results for the time to regain birth weight are shown in Table 3. Infants receiving rapid advancement were

1.8 times more likely to regain birth weight earlier than the slow advancement of enteral feeds (hazard 1.77, p = 0.001, 95% CI 1.26–2.5). There was no evidence of an interaction effect from either high or low initiation volumes; therefore the beneficial effect of rapid advancement occurred irrespective of the enteral initiation volume. There was evidence of non proportional hazards (p = 0.04), therefore the data were split according to median time to regain birth weight (13 days); infants receiving rapid advancement were more than twice as likely to regain their birth weight before 13 days than infants receiving slow advancement of enteral feeds but this effect was not statistically significant after 13 days. There was no evidence of non-proportional hazards after splitting the time period.

Figure 4 shows the Kaplan-Meier plot showing the time to discharge. The effects of feeding strategies on the time to discharge are shown in Table 4. There was no significant effect of either high initiation volume or rapid advancement of feeds when examining the interventions separately and assuming proportional hazards. There was evidence of an interaction between the interventions and of non-proportional hazards for the effect of rapid advancement (p = 0.05). We therefore split the data according to the median time to discharge (58 days); rapid advancement of feeds was associated with shorter discharge times but this effect was not significant after 58 days.

No significant differences in length gain or head circumference gain were noted with or without interaction, as seen in Table 5.

Secondary outcomes: mortality and morbidity

No differences were noted in any of these outcomes, as seen in Table 5. The treatment interaction was not tested for NEC due to small numbers; there was no evidence of a treatment interaction for other outcomes in table 5 ($p > 0.1$). The morbidity and mortality for all four groups are shown in Table 6. The mortality rate for the entire cohort before discharge was 31%. NEC occurred in 9.5%; feed interruptions at any time occurred in 41%; PN was received by 12%; and late onset sepsis occurred in 16% of the infants.

Discussion

The data from our study, suggest that ELBW infants, can tolerate higher initiation feed volumes and larger daily increments than have previously been described in infants ≤ 1000 g. This enteral feeding practice does not appear to increase the risk for mortality or feed-related morbidity, including NEC. High initiation and rapid advancement of enteral feed volumes

was associated with a significantly faster time to achieve a weight of 1500 g. Rapid advancement of enteral feeds resulted in a significantly faster time to regain birth weight and the duration of hospital stay in these infants was significantly lower. The statistical significance of these time-to-event outcomes decreased with time, this suggests that a degree of catch-up growth occurs in the longer stay infants, and most benefit may be obtained in a setting where early discharge and/or KMC is practiced. Slow advancement of enteral feeds results in delayed establishment of full enteral feeds.[13, 14] It is recognized that preterm infants, particularly ELBW infants receiving PN are at risk of cholestasis and infection. [20] In our study the incidence of these feed-related morbidities was not increased – although the sample was not sufficiently powered to draw firm conclusions from these data. The lack of routine PN use, make the findings particularly relevant to resource-limited settings where PN is not routinely available.

Our study is unique; it is the largest RCT comparing feeding strategies in ELBW infants to date; it is the only study to examine both the volume of initiation and the volume of advancement. Importantly, our study exclusively enrolled infants ≤ 1000 g, a previously under-represented group who are at high risk for NEC. However, our study has several limitations; all the infants received exclusive breast milk until they weighed 1200 g, it would be inappropriate to extrapolate our findings to infants fed with formula milk. The trial was not sufficiently powered to detect statistically significant differences in NEC and mortality. Blinding of the intervention to the clinicians was not possible due to the nature of the intervention and the clinicians reviewing the abdominal radiographs were not blinded to the randomized group. The study did not include long-term follow-up, hence the later effects of improved early weight gain in this setting are unknown. Finally, resource constraints prohibited the routine use of PN; it is unclear whether the use of PN could have influenced the growth outcomes by reducing the early protein deficit.

The incidence of NEC has remained unchanged during the past 20 years, presumably because improvements in neonatal intensive care have resulted in improved early neonatal survival rates, particularly in ELBW infants.[21] Many infants who develop NEC have received enteral feeds and the early introduction and rapid advancement of enteral feeds have previously been implicated in the pathogenesis of NEC.[22,23] The timing, volume of the initiation as well as the rate of advancement of enteral feeds may collectively or independently have the potential to determine important outcomes such as NEC, late-onset sepsis and long-term neurodevelopment outcomes.[21] Our data are in keeping with findings of five RCT's and the

Cochrane meta-analysis; suggesting that the practice of low volume increment feed advancement (≤ 20 ml/kg/day) does not reduce the risk for developing NEC.[6, 9-13] Similar to our study, the meta-analysis found that advancing the feeds at a slow rate also resulted in a delay in the time taken to regain birth weight and to establish full enteral feeds.[13] This review did not examine volume of initiation of feeds in the way that we did; but in a Cochrane review, Bombell et al. did not find any evidence that trophic feeds affected feed tolerance, growth rates or the risk for NEC.[24] In a separate Cochrane review, delaying the introduction of feeds did not prevent NEC.[25] We similarly did not find a difference in the incidence of NEC when only comparing the volume of initiation; the incidence of NEC in our study of 9.5% was slightly lower to our previous reports of 9.9%.[26]

The main finding of our study was that higher initiation feed volumes and larger daily feed increments in infants with a birth weight of ≤ 1000 g improved short-term weight gain, decreased hospital stay and was well-tolerated – this finding should be considered in future feeding protocols and studies. Further large RCTs are needed to determine the short-term and long-term effect of including PN in early aggressive enteral feeding strategies, on outcomes such as NEC, particularly in more premature infants.

Conflict of Interest

None

Declaration of funding source

None

Figure 1: Flow of patients

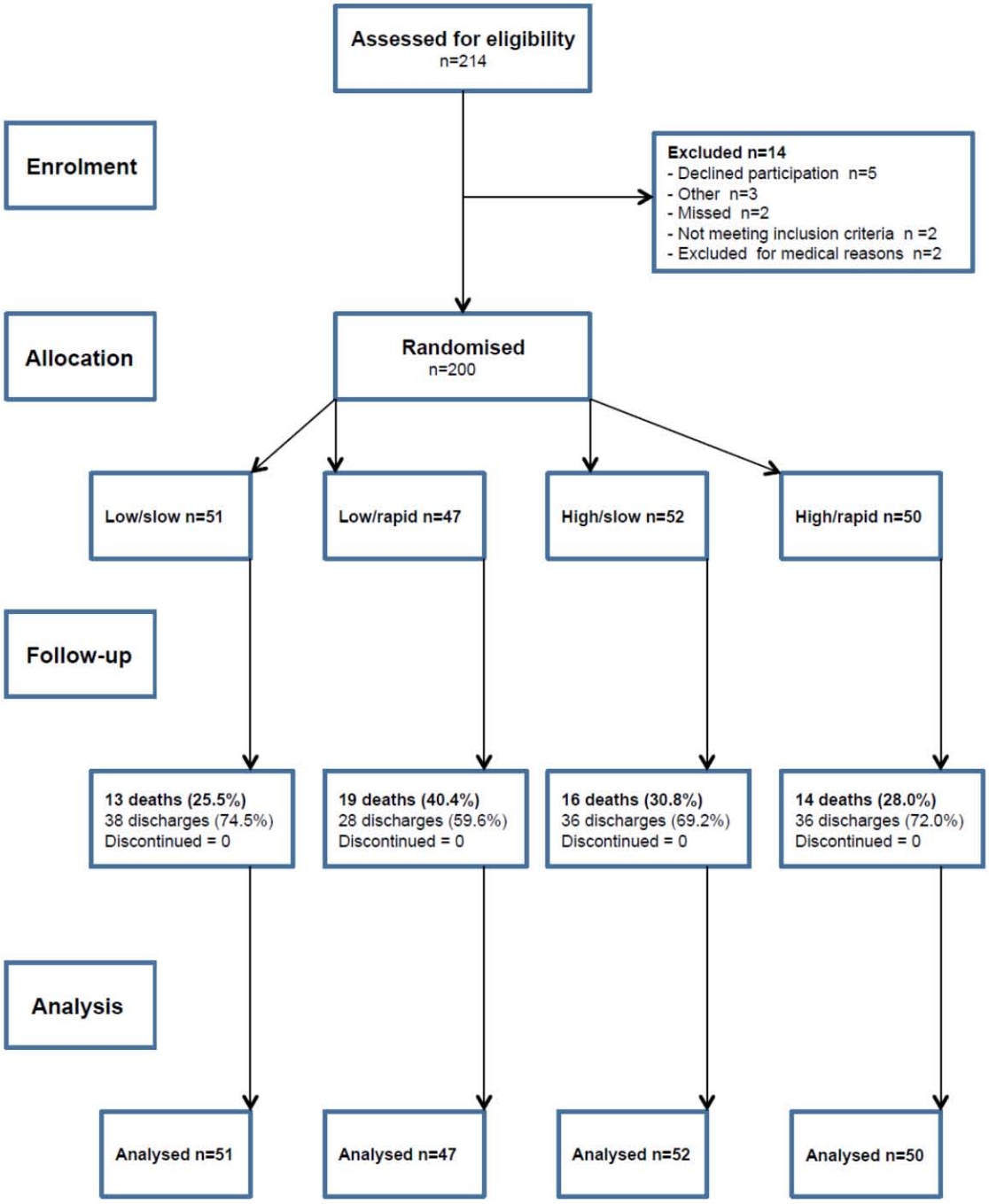

Figure 2: Time to attain 1500 g (all 4 groups)

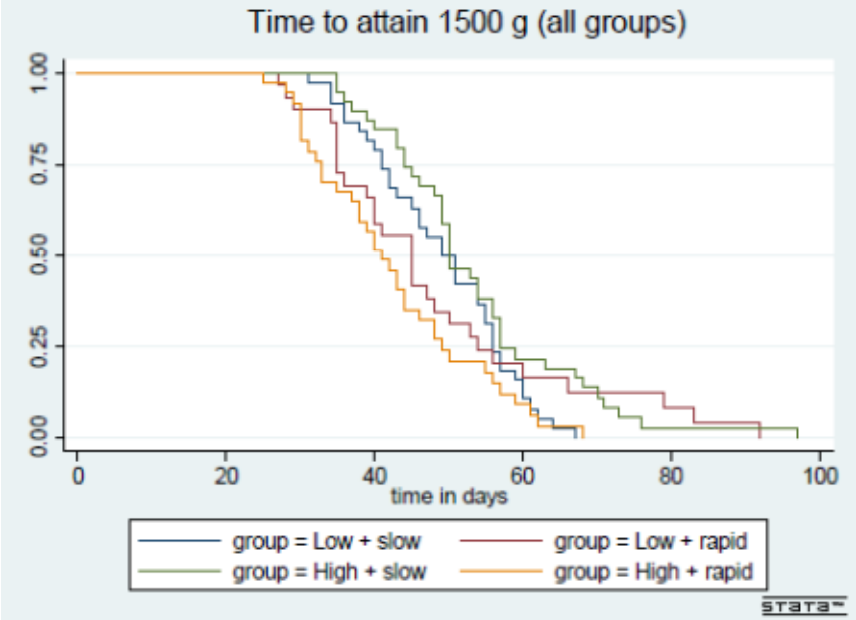

Figure 3: Time to regain birth weight (all 4 groups)

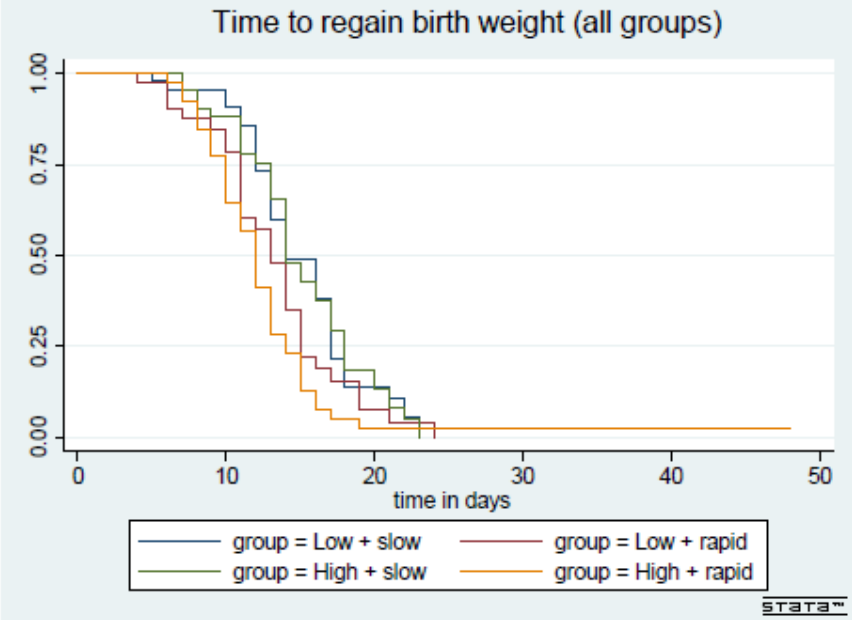

Figure 4: Time to discharge (all 4 groups)

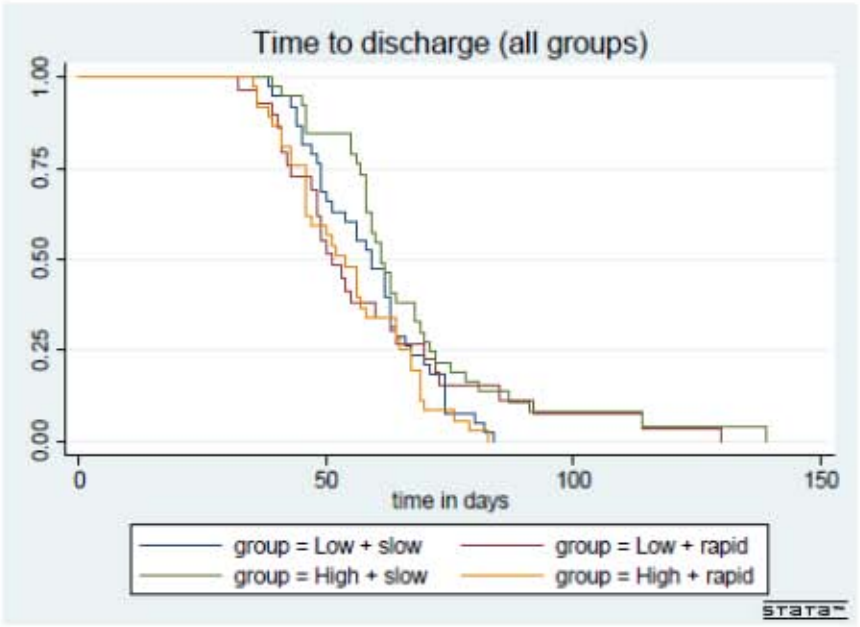

Table 1: Variables in the study patients[a]

Demographic variables	**Low/Slow** n=51, n (%)[b]	**Low/Rapid** n=47, n (%)[b]	**High/Slow** n=52, n (%)[b]	**High/Rapid** n=50, n (%)[b]
Pregnancy induced hypertension	29 (57)	32 (68)	35 (67)	40 (80)
Multiple pregnancy				
Twins	4 (7.8)	7 (15)	4 (7.7)	4 (8.0)
Triplets	2 (3.9)	0	0	0
Onset of labour				
Spontaneous labour	11 (21.6)	9 (19.1)	12 (23)	8 (16)
Unmonitored induction of labour	2 (3.9)	2 (4.3)	2 (3.8)	3 (6)
Caesarean section	38 (74.5)	36 (76.6)	38 (73.1)	39 (78)
Gestation at delivery				
Mean (SD)	28.7 (1.6)	28.9 (2.5)	29.0 (1.9)	29.1 (2.0)
< 29 weeks	26 (51)	26 (55)	20 (38.5)	21 (42)
≥ 29 weeks	25 (49)	21 (45)	32 (61.5)	29 (58)
Male	22 (43.1)	21 (44.7)	20 (38.5)	23 (46)
Birth weight, g				
Mean (SD)	845 (114.5)	858.5 (105)	833 (95)	853.5 (116)
< 600 g	1 (2)	0	1 (1.9)	1 (2)
600 - 749 g	9 (17.6)	8 (17)	9 (17.3)	12 (24)
750 – 1000 g	41 (80.4)	39 (83)	42 (80.8)	37 (74)
Mean 1 minute Apgar (SD)	5.6 (2.9)	5.5 (2.5)	5.4 (2.7)	5.9 (2.7)
Mean 5 minute Apgar (SD)	7.5 (2.6)	7.6 (2.1)	7.5 (1.9)	7.9 (2.1)
Positive pressure ventilation	7 (13.7)	2 (4.3)	4 (7.7)	1 (2)
Nasal continuous airway pressure	39 (76.5)	38 (80.9)	46 (88.5)	43 (86)
Maternal HIV	9 (17.6)	13 (27.6)	13 (25.0)	12 (24.0)
Antenatal steroids	32 (62.7)	31 (66.0)	31 (59.6)	26 (52.0)
IUGR	32 (62.7)	29 (61.7)	37 (71.2)	35 (70.0)
Number of days to attain 1500g				
Median (IQR)	50.0 (41-56)	45.0 (35-53.5)	50.0 (44.5-57)	41.0 (33-49)
Number of days to regain birth weight				
Median (IQR)	14.0 (12-17)	12.5 (10-14.5)	14.0 (11.5-18)	12.0 (10-14)
Number of days to discharge				
Median (IQR)	59.0 (49-67)	50.5 (42.5-67)	61.0 (56.5-70.5)	52.0 (43-67)

a, there were no statistically significant differences between the four allocation groups; b, unless otherwise specified; HIV – human immunodeficiency virus; IUGR – intrauterine growth restriction; SD – standard deviation; IQR –interquartile range (25^{th}-75^{th} percentile)

Table 2: Primary outcome: time to attain a weight of 1500 g

Study Group	Hazard Ratio	P value	95% CI
Model 1: Without interaction[a]			
High vs Low	1.05	0.75	0.75 – 1.50
Rapid vs Slow	1.48	0.03	1.05 – 2.09
Model 2:With interaction[a]			
High/Slow vs Low/Slow	0.73	0.19	0.46 – 1.16
Low/Rapid vs Low/Slow	0.96	0.86	0.57 – 1.59
High/Rapid vs Low /Slow	1.62	0.05	1.01 – 2.59
Model 3: Split time period with interaction [b]			
High/Slow vs Low/Slow (whole time period)	0.70	0.14	0.43 – 1.12
Low/Rapid vs Low/Slow (before 47 days)	1.48	0.21	0.80 – 2.73
Low/Rapid vs Low/Slow (after 47 days)	0.59	0.11	0.31 – 1.12
High/Rapid vs Low/Slow (before 47 days)	2.29	0.003	1.32 – 3.97
High/Rapid vs Low/Slow (after 47 days)	0.91	0.77	0.46 – 1.77

a, Interaction - the effect of low vs. high volume initiation varies with rate of advancement;
b, Split time period - hazard ratios for the effect of rapid advancement was not constant over time, hence data was split according to before or after the median time to attain a weight of 1 500g (47 days).

Table 3: Time to regain birth weight

Study Group	Hazard Ratio	P value	95% CI
Model 1: Without interaction[a]			
High vs Low	1.17	0.35	0.84 – 1.63
Rapid vs Slow	1.77	0.001	1.26 – 2.50
Model 2:With interaction[a]			
High/Slow vs Low/Slow	1.02	0.93	0.65 – 1.60
Low/Rapid vs Low/Slow	1.52	0.09	0.93 – 2.48
High/Rapid vs Low /Slow	1.35	0.38	0.70 – 2.60
Model 3: Split time period without interaction [b]			
High vs Low	1.16	0.38	0.83 – 1.61
Rapid vs Slow (before 13 days)	2.26	0.001	1.42 – 3.60
Rapid vs Slow (after 13 days)	1.29	0.37	0.75 – 2.21

a, Interaction - the effect of low vs. high volume initiation varies with rate of advancement;
b, Split time period - hazard ratios for the effect of rapid advancement was not constant over time, hence data was split according to before or after the median time to attain a birth weight (13 days).

Table 4: Time to discharge

Study Group	Hazard Ratio	P value	95% CI
Model 1:Without interaction[a]			
High vs Low	0.96	0.80	0.69 – 1.35
Rapid vs Slow	1.37	0.08	0.97 – 1.93
Model 2: With interaction[a]			
High/Slow vs Low/Slow	0.69	0.12	0.43 – 1.10
Low/Rapid vs Low/Slow	0.94	0.82	0.57 – 1.57
High/Rapid vs Low/Slow	1.33	0.23	0.83 – 2.11
Model 3: Split time period without interaction[b]			
High vs Low	0.91	0.60	0.65 – 1.29
Rapid vs Slow (before 58 days)	1.92	0.006	1.21 – 3.05
Rapid vs Slow (after 58 days)	0.86	0.60	0.49 – 1.49
Model 4: Split time period with interaction[b]			
High/Slow vs Low/Slow (whole time period)	0.66	0.09	0.41 – 1.07
Low/Rapid vs Low/Slow (before 58 days)	1.34	0.33	0.74 – 2.45
Low/Rapid vs Low/Slow (after 58 days)	0.62	0.14	0.32 – 1.18
High/Rapid vs Low/Slow (before 58 days)	1.77	0.04	1.03 – 3.03
High/Rapid vs Low/Slow (after 58 days)	0.81	0.53	0.42 – 1.57

a, Interaction - the effect of low vs. high volume initiation varies with rate of advancement;
b, Split time period - hazard ratios for the effect of rapid advancement was not constant over time, hence data was split according to before or after the median time to discharge (58 days).

Table 5: Secondary outcomes: morbidity and mortality comparisons without interaction[a]

Outcomes	Odds Ratio[b]	P value	95% CI
NEC			
High vs Low	1.35	0.54	0.51 – 3.57
Rapid vs Slow	1.00	0.99	0.38 – 2.64
Mortality			
High vs Low	0.85	0.60	0.46 – 1.60
Rapid vs Slow	1.33	0.40	0.72 – 2.50
Feed interruptions			
High vs Low	1.10	0.74	0.63 – 1.94
Rapid vs Slow	0.86	0.60	0.50 – 1.50
Parenteral nutrition			
High vs Low	0.80	0.60	0.32 – 1.83
Rapid vs Slow	0.76	0.50	0.32 – 1.82
Late-onset sepsis			
High vs Low	0.70	0.40	0.32 – 1.50
Rapid vs Slow	0.70	0.30	0.32 – 1.50
Head growth			
High vs Low	-1.7[c]	0.84	-16.7 – 16.1
Rapid vs Slow	2.2[c]	0.80	-13.6 – 1.21
Length growth			
High vs Low	0.16[c]	0.84	0.18 – 0.15
Rapid vs Slow	0.22[c]	0.80	0.15 – 0.20

a, Interaction - the effect of low vs. high volume initiation on rapid advancement; b, unless otherwise specified;
c, percentage difference in growth from birth to discharge comparing treatment groups; NEC- necrotising enterocolitis; PN- parenteral nutrition

Table 6: Secondary outcomes: morbidity and mortality[a]

Outcomes	**Overall** n=200 n (%)	**Low/Slow** n=51, n (%)	**Low/Rapid** n=47, n (%)	**High/Slow** n=52, n (%)	**High/Rapid** n=50, n (%)
NEC	19 (9.5)	1 (2.0)	7 (15)	9 (17)	2 (4)
Mortality to discharge	62 (31.0)	13 (25.5)	19 (40.4)	16 (30.8)	14 (28.0)
No. of infants with feed interruptions	82 (41)	20 (39.2)	19 (40.4)	24 (46.2)	19 (38)
Infants requiring PN	24 (12)	6 (11.8)	7 (14.9)	8 (15.4)	3 (6.0)
Late-onset sepsis	32 (16)	9 (17.6)	9 (19.1)	10 (19.2)	4 (8.0)

a, there were no statistically significant differences between the four allocation groups; PN – parenteral nutrition; NEC- necrotising enterocolitis

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Part D: Appendices

Appendix 1

Letter of approval from research ethics committee

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • Facsimile [021] 406 6411
sumayah.ariefdien@uct.ac.za

26 July 2011

HREC REF: 283/2011

Dr MS Raban,
Neonatology
H46, OMB

Dear Dr Raban,

PROJECT TITLE: RAPID VERSUS SLOW RATE ADVANCEMENT OF FEEDS FOR ENTERALLY FED EXTREMELY LOW BIRTH WEIGHT INFANT ≤ 1000G :RANDOMISED CONTROLLED TRIAL

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 28 July 2012

Please submit an annual progress report (FHS016) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

pp **PROFESSOR MARC BLOCKMAN**
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 2 - Data Capture Sheet

Low volume initiation + slow advancement (data collection)

Patients sticker:

Ballard gestation:	Birth Weight:	HC at birth:
IUGR (<10th): Y/N	RVD exposed: Y/N	
48 hrs maternal steroids: Y/N	Mode of delivery:	
Indication for early delivery:	APGARS 1: 5:	
Doses of surfactant:	Initial respiratory support:	
NEC: Y/N	Max weight loss:	
Discharge Weight:	Discharge date:	

Feeding Regime

Day 1	4ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 2	12ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 3	36ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day4	60ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 5	84ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 6	108ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 7	132ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 8	156ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 9	180ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 10	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt

Feed interruptions

Date:

Appendix 3 - Data Capture Sheet

Low volume initiation + rapid advancement (data collection)

Patients sticker:

Ballard gestation:	Birth Weight:	HC at birth:
IUGR (<10th): Y/N	RVD exposed: Y/N	
48 hrs maternal steroids: Y/N	Mode of delivery:	
Indication for early delivery:	APGARS 1: 5:	
Doses of surfactant:	Initial respiratory support:	
NEC: Y/N	Max weight loss:	
Discharge Weight:	Discharge date:	

Feeding Regime

Day 1	4ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 2	40ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 3	76ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day4	112ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 5	148ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 6	184ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 7	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 8	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 9	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 10	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt

Feed interruptions

Date:

Appendix 4 - Data Capture Sheet

High volume initiation + slow advancement (data collection)

Patients sticker:

Ballard gestation:	Birth Weight:	HC at birth:
IUGR (<10th): Y/N	RVD exposed: Y/N	
48 hrs maternal steroids: Y/N	Mode of delivery:	
Indication for early delivery:	APGARS 1: 5:	
Doses of surfactant:	Initial respiratory support:	
NEC: Y/N	Max weight loss:	
Discharge Weight:	Discharge date:	

Feeding Regime

Day 1	24ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 2	24ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 3	48ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day4	72ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 5	96ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 6	120ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 7	144ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 8	168ml/kg/day	……..ml EBM/DEBM/formula	iv volume… Wt
Day 9	192ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 10	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt

Feed interruptions

Date:

Appendix 5 - Data Capture Sheet

High volume initiation + rapid advancement (data collection)

Patients sticker:

Ballard gestation:	Birth Weight:	HC at birth:
IUGR (<10th): Y/N	RVD exposed: Y/N	
48 hrs maternal steroids: Y/N	Mode of delivery:	
Indication for early delivery:	APGARS 1: 5:	
Doses of surfactant:	Initial respiratory support:	
NEC: Y/N	Max weight loss:	
Discharge Weight:	Discharge date:	

Feeding Regime

Day 1	24ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 2	60ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 3	96ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day4	132ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 5	168ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 6	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 7	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 8	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 9	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt
Day 10	200ml/kg/day	……..ml EBM/DEBM/formula	iv volume…. Wt

Feed interruptions

Date:

Appendix 6

PARENTAL INFORMATION AND CONSENT FORM FOR MPHIL (NEONATOLOGY)

Research Title: Rapid versus slow rate advancement of feeds for oral fed extremely low birth weight infants ≤1000g: a randomised controlled trial

Principal Investigator: Dr MS Raban
021-4044239/0823124819 Email: shukriraban@yahoo.co.uk

Invitation

You are being invited to enrol your baby in a research study. Before you decide whether or not to participate, it is important for you to understand why the research is being done and what it will mean for your baby. Please take time to read the following information carefully.

Why is this study being done?

We do not know what the best way is to feed small, preterm babies weighing less than 1000g.

In the past, milk feeds by mouth were only started a few days after the baby was born then increased slowly. Studies have shown that this way of feeding caused the babies to grow slower and take longer to get to full feeds by mouth.

More recent studies show that faster feeding is safe for babies without increasing complications.

The possible benefits of feeding babies faster are that the babies may grow better, have less infections and stay in hospital for a shorter time.

This study aims to show that by starting milk feeds on the 1st day of life and increasing them more quickly, the babies will grow better, takes less days to take the full milk amount by mouth and possible a shorter hospital stay.

Why have I been asked to take part?

You have been approached because your baby weighs less than or equal to 1000g.

Do I have to take part?

Participation in this study is entirely voluntary. It is up to you to decide whether or not to take part in this study. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form.

Who is doing the study?

This medical study is done by a group of researchers from the Department of Neonatology at Groote Schuur Hospital and from Imperial College London.

The person responsible for directing the research is Dr M Shukri Raban

What will happen to my baby if we participate?

If you agree to take part in the study, the doctor looking after your baby will telephone Dr Raban. With the help of a computer program, Dr Raban will place your baby in one of 4 groups.

- In the first group, your baby's milk feeds will be started with a small amount (4ml/kg) then increased slowly everyday by 24ml/kg/day
- In the second group, your baby's milk feeds will be started with a small amount (4ml/kg) then increased fast everyday by 36ml/kg/day
- In the third group, your baby's milk feeds will be started with a high amount (24ml/kg) then increased slowly everyday by 24ml/kg/day
- In the fourth group, your baby's milk feeds will be started with a high amount (24ml/kg) then increased fast everyday by 36ml/kg/day

How many people will participate and how long does the research last?

Up to 200 mothers will be asked to take part in the study. Your baby will continue in the study up until he/she is discharged from hospital.

How will my baby be fed?

Breast milk is the best milk. Every mother should be encouraged to provide breast milk to their babies. If breast milk is unavailable, the baby will receive donated pasteurised breast milk.

What is donated pasteurised breast milk?

It is milk donated by other mothers who are breast feeding their own babies, which has been pasteurised and then frozen.

What is pasteurisation?

It is a process where the milk is heated to 62.5oc for 30 minutes.

Can your baby get an infection or HIV from this milk?

The process of pasteurisation is known to kill the HIV virus as well as other germs which may cause infection

What happens if there is no mother's breast milk or donor breast milk?

Breast milk is the best milk. If there is no mother's milk or donated breast milk, your baby will receive a formula feed, which is also a safe and appropriate way of feeding preterm babies.

Are the donor mothers tested for HIV?

Yes, all donor mothers are tested for HIV.

How will my baby be cared for during the study?

Your baby will be cared for and looked after in the same that the doctors and nurses were caring for babies before the study started.

What will happen to my baby if I do not take part in the study or I withdraw my baby from the study?

Your baby will be cared for and treated the same way as all the other babies. Breast milk will still be encouraged, donor human breast milk will be used with your consent and formula will be used as a substitute if no breast milk is available.

Will your information be kept confidential?

Every effort will be made to keep the information of your baby private, throughout the research period and after it is finished. Nobody other than the research clinicians who enrol your baby into the research project will know that you are a participant.

The researchers will consider baby's records private to the extent permitted by the law. These records may also be reviewed by the University of Cape Town Human Research Ethics Committee which protects the rights of people participating in research. They will ensure the information is kept confidential, as required by law.

What if something happens, or if you have any questions about your rights, in the research project?

This research will be monitored by the Human Research Ethics Committee of the University of Cape Town.

During the research you may contact either the Human Research Ethics Committee (021-4066492) or Dr Raban (0214044239) if you have further questions or concerns.

The decision to allow your baby to participate in this study is entirely your own. A decision not to participate will not affect your baby's future healthcare.

Appendix 7

Consent Form

I have read and discussed this form with the researchers and understand what the research project titled "Rapid versus slow rate advancement of feeds for enterally fed extremely low birth weight infants ≤1000g: a randomised controlled trial" is about.

My questions have been answered.

I freely agree to: (tick the appropriate block)

☐ I agree to take part in the above study.

☐ I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions.

☐ I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason.

☐ I agree that my data gathered in this study may be stored in a specialist data centre and may be used for future research

☐ I consent to my baby receiving Donated Pasteurised Breast Milk

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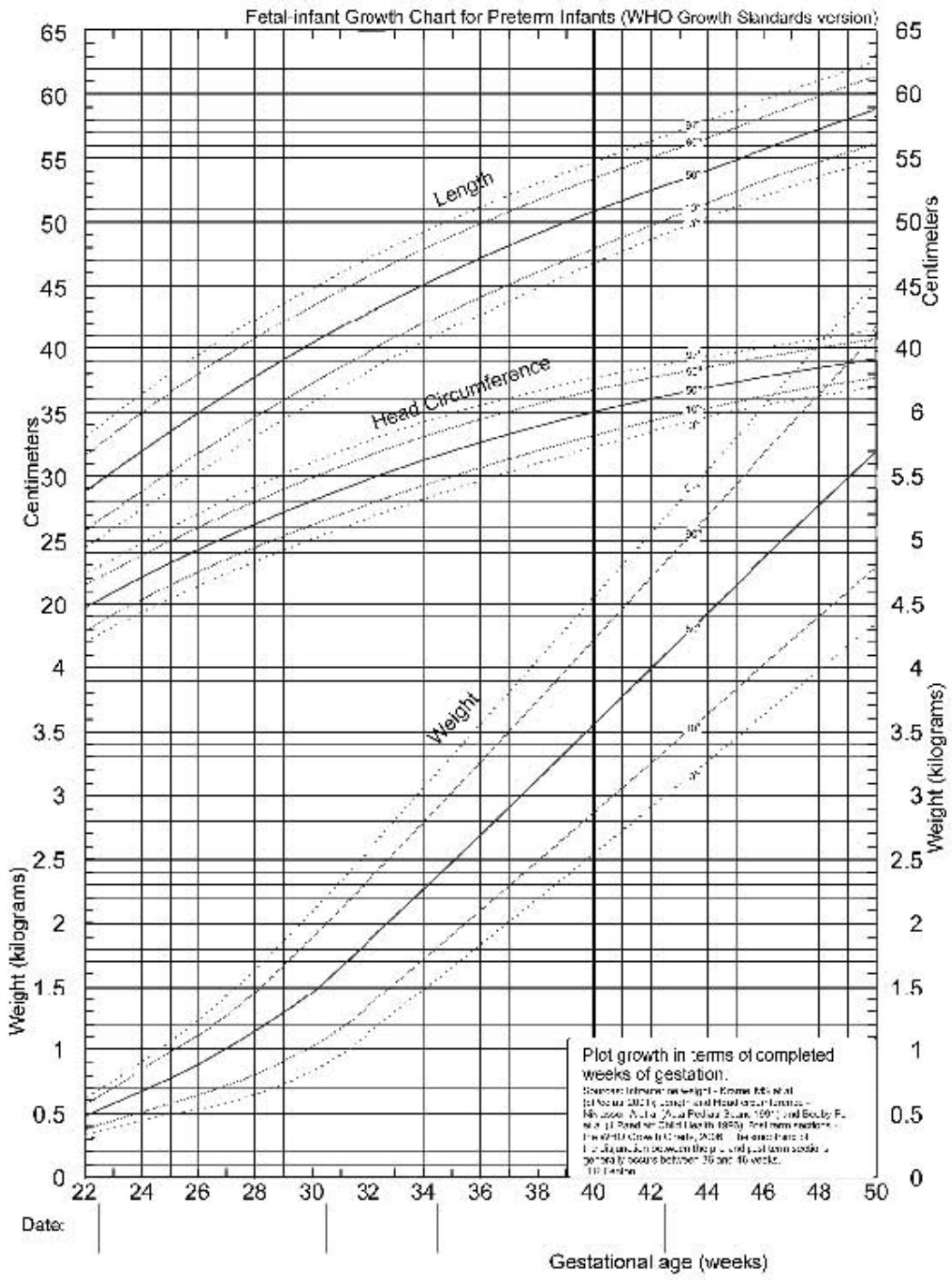
Name of Mother	Signature	Date

----------	----------	----------
Name of research clinician	Signature	Date

----------	----------	----------
Name of Witness	Signature	Date

Appendix 8 – Fenton growth chart



Appendix 9

Serious adverse event form (SAEF)

1. Contact information

Clinician completing this form

Name:

Position:

Email:

Phone:

2. Date of SAE report and study information

Date reported:

Principal investigator:

Project title:

Person to who report forwarded to:

3. SAE description

Patient folder number:

Patient name:

Date event noted:

Brief Description:

4. SAE category (please circle as applicable)

Not related the SAE is completely independent from the study; and/or evidence exists that the event has another aetiology

Possibly related less clear temporal association; other aetiologies are also possible

Probably relatedclear temporal association, and a potential alternative aetiology is not apparent

Definitely related clear temporal association and no other cause possible

5. SAE outcome

Action taken:

Response:

Appendix 10

Contributors' Statement Page

M Shukri Raban: As the principal investigator, Dr Raban contributed to the conceptualization, and design of the study; coordinated the recruitment of study patients and supervised the data collection; drafted the initial manuscript and approved the final manuscript as submitted.

Shalini Santhakumaran: Ms Santhakumaran planned and carried out analysis of the data, reviewed the manuscript and approved the final manuscript as submitted.

Quanitah Keraan and Yaseen Joolay: Drs Keraan and Joolay coordinated the recruitment of study patients and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

Alan R Horn, Sabita Uthaya, Neena Modi and Michael C Harrison: Professors Horn, Modi, and Harrison, and Dr Uthaya; contributed to the conceptualisation and design of the study, assisted with the analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Appendix 11

Cover Letter

Dr M Shukri Raban
Department of Neonatology
University of Cape Town
H46 Old Main Building
Groote Schuur Hospital,
Private Bag, Observatory
Cape Town
South Africa
7935
shukriraban@yahoo.co.uk

Dear Editor-in-Chief
University of Vermont College of Medicine
89 Beaumont Ave
Given Courtyard, S261
Burlington, VT 05405

Date:

Dear Editor

We hereby submit a manuscript entitled "**High or low enteral feed volume initiation followed by rapid or slow advancement of enteral feeds for extremely low birth weight infants: a randomised controlled trial"** by MS Raban, S Santhakumaran, Q Keraan, Y Joolay, S Uthaya, AR Horn, N Modi and MC Harrison to be considered for publication as an original article in *Pediatrics*.

This research is unique; it is the first feeding trial which exclusively recruited infants weighing ≤ 1000 g. In addition, it is also the first feeding trial to examine the effect of both the size of the initiation enteral volumes and the advancement rate as separate components. This article adds value to the current body of evidence. It demonstrates that a higher initiation enteral feed volume (24 ml/kg/day) and rapid advancement (36 ml/kg/day) was well tolerated without an increased risk for mortality, necrotising enterocolitis or late-onset sepsis. Importantly, the high initiation volume and rapid advancement feeding regime resulted in increased early weight gain and decreased the length of hospital stay. We believe these findings will be of interest to the readers of your journal.

We declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We wish to confirm that there are no known conflicts of interest associated with the publication and there has been no financial support for this work that could have influenced its outcome. The manuscript has been read and approved by all the named authors.

We hope you find the manuscript suitable for publication and look forward to hearing from you.

Sincerely,

Dr M Shukri Raban

Appendix 12

Title Page

High or low enteral feed volume initiation followed by rapid or slow advancement of enteral feeds for extremely low birth weight infants: a randomised controlled trial

M Shukri Raban[1], FCPaed (SA), Cert Neonatology (SA); Shalini Santhakumaran[2], MSc (London School of Hygiene and Tropical Medicine); Quanitah Keraan[1], FCPaed (SA); Yaseen Joolay[1], FCPaed (SA), MPhil Neonatology (UCT), Cert Neonatology (SA); S Uthaya[2], MBBS, MD, MRCP (UK), FRCPCH (UK); Alan R Horn[1], FCPaed (SA), Cert Neonatology (SA), PhD (UCT); Neena Modi[2], MD (University of Edinburgh), FRCP (London), FRCPCH (UK); Michael C Harrison[1], MRCP (UK), FRCPCH (UK)

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Short title: High feed volume initiation and rapid advancement in extremely low birth weight infants

Abbreviations: BMF – breast milk fortifier; DEBM – donor human breast milk; EBM – expressed human breast milk ; ELBW – extreme low birth weight infants weighing < 1000 g; KMC – kangaroo mother care; MEF – minimal enteral feeding; NEC– necrotising enterocolitis; NPO– nil by mouth; PN – parenteral nutrition; RCT – randomised controlled trial; VLBW-very low birth weight infant

Key Words: enteral feeding, infant premature, infant, very low birth weight, necrotising enterocolitis, enteral nutrition, newborn

Funding Source: No funding was secured for this study.

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Clinical Trial Registration: The trial has been registered with the ISRCTN Register (http://isrctn.org) (identifier ISRCTN96923718).

What's Known on This Subject: Wide variation exists in the initiation and rate of advancement of enteral feeds in preterm infants. Randomised controlled trials and meta-analyses have not demonstrated increased risk of NEC, but the trials were insufficiently powered to inform management in ELBW infants.

What This Study Adds: Early introduction of enteral feeds in ELBW infants; at initiation volumes of 24ml/kg/day and advancement at 36ml/kg/day; results in improved weight gain and fewer days in hospital. This feeding strategy does not appear to increase the risk for NEC.

Appendix 13

Pediatrics author guidelines

Author Guidelines

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Introduction

Pediatrics is the official peer-reviewed journal of the American Academy of Pediatrics. *Pediatrics* publishes original research, clinical observations, and special feature articles in the field of pediatrics, as broadly defined. Contributions pertinent to pediatrics also include related fields such as nutrition, surgery, dentistry, public health, child health services, human genetics, basic sciences, psychology, psychiatry, education, sociology, and nursing. *Pediatrics* is the most-cited journal in the field of pediatrics, with a 2010 impact factor of 5.391, and a circulation of 66,000. It is translated in full or in part into four languages, Spanish, Polish, Chinese, and Portuguese.

Pediatrics considers unsolicited manuscripts in the following categories: reports of original research, particularly clinical research; review articles; special articles; and case reports. When preparing a manuscript for *Pediatrics*, authors must first determine the manuscript type and then prepare the manuscript according to the specific instructions below.

The electronic edition of *Pediatrics* is the journal of record. Some accepted articles may also be presented in full in the print version. The editors reserve the right to determine whether an accepted manuscript will be published in the print edition in addition to the electronic edition of *Pediatrics*.

Acceptance Criteria

Relevance to readers is of primary importance in manuscript selection. The readership includes general and specialist pediatricians, pediatric researchers and educators, and child health policymakers. *Pediatrics* receives many more high quality manuscripts than can be accommodated based on our available space. The current acceptance rate is approximately 10%. An article that is thought by the editors to be not relevant to readers, outside of scope or very unlikely to be accepted may be rejected without review. All manuscripts considered for publication are peer reviewed. Peer reviewers are selected by the editors based on their expertise in the topic of the manuscript; generally at least 2 reviews are required before a decision is rendered. Authors may suggest appropriate reviewers and may also suggest reviewers who should not review the manuscript.

Authors should carefully follow instructions for manuscript preparation, and ensure that the manuscript is proofread before submission. Manuscripts that do not adhere to the author instructions will not be considered for review. Careless preparation of a manuscript suggests careless execution of the research and therefore makes acceptance unlikely. Manuscripts are scanned for plagiarism using the latest software; if potential plagiarism is detected, the editors will contact the authors for clarification, and may also contact the authors' institution.

Submissions of original research are judged on the importance and originality of the research, scientific strength, clinical relevance, the clarity of the manuscript, and the number of submissions on the same topic.

Pediatrics accepts review articles, with preference given to systematic reviews, which may include meta-analyses. State-of-the-Art Review Articles and Perspectives are generally solicited by the editors or the associate editors for their respective sections. Special Articles reflect topics or issues of relevance to pediatric health care that do not conform to a traditional study format. Case Reports must challenge an existing clinical or pathophysiologic paradigm; provide a starting point for novel hypothesis-testing clinical research; and/or offer a clinical lesson. Quality Reports provide a venue for manuscripts that describe the implementation and outcome of quality-improvement projects. Authors should review and follow the comprehensive reporting guidelines for a wide variety of study designs that are available at http://www.equator-network.org/home/.

Authors submitting manuscripts involving adverse drug or medical device events or product

problems should also report these to the appropriate governmental agency.

Pediatrics does not publish manuscripts that involve animal research.

Unsolicited commentaries will be considered for publication; however, most commentaries are solicited by the editors. Responses to a published article should be submitted as eLetters (see this section); selected eLetters may be published in the journal as Letters to the Editor.

Incorrect grammar, language use, or syntax may distract readers from the science being communicated and may lead to less favorable reviews. To help reduce this possibility, we strongly encourage authors to have their manuscripts reviewed for clarity by colleagues. If the authors' native language is not English, we strongly encourage review and editing by a colleague whose native language is English or the use of an English language editing service.

Peer reviewers are asked to assess each manuscript for originality; for interest to scientists, practitioners and policy makers; for quality of the analysis; and for quality of the presentation, and are asked to assess the priority of the paper for publication. After the reviews are received, the editors may take one of the following actions: *Accept*; *Accept with Revisions*; *Reject with option to Resubmit*; or *Reject*. A rejected manuscript may not be resubmitted. A manuscript may be rejected with an option to resubmit when additional data or analyses are requested by reviewers, or when extensive revision of the text is needed. The resubmitted manuscript receives an additional round of peer review (which may include new reviewers), and the manuscript may or may not be accepted. A decision of *Accept with Revision* indicates that the editors intend to accept the manuscript contingent on adequate response to reviewers. A decision of Accept (which is exceedingly rare on first submission) indicates that the manuscript is ready to place into production without further modification. Decisions by the editors are final.

Publication Ethics

Authorship. An "author" is someone who has made substantive intellectual contributions to a published study. Each author is required to meet ALL THREE of the following criteria:

1) Substantial contribution(s) to conception and design, acquisition of data, or analysis and interpretation of data; and
2) Drafting the article or revising it critically for important intellectual content; and
3) Final approval of the version to be published.

NOTE: Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute a sufficient basis for authorship.

All persons listed as authors must meet these criteria, and all persons who meet these criteria must be listed as authors. Although *Pediatrics* does not specifically limit the number of authors (except for Case Reports), articles submitted with an unusual number of authors invite scrutiny by editors and reviewers for clear justification for the presence of each person on the authorship list. *Pediatrics* does not permit more than one author to claim any particular position in the author list (e.g., two first authors, or two senior authors). Decide authorship issues, including the order, before submission. **After submission, any authorship changes require the written approval of all authors.**

Conflict of Interest and Disclosure. After a paper is accepted by *Pediatrics* for publication, all authors must submit conflict of interest and disclosure forms. *Pediatrics* adheres to the policy and uses the standardized disclosure form of the International Committee of Medical Journal Editors (ICMJE). The collection of the forms is automated within the online system.

IRB Approval. All studies that involve human subjects must be approved or deemed exempt by

an official institutional review board; this should be noted in the Methods section of the manuscript.

Industry Sponsorship. *Pediatrics* generally does not accept reports of studies in which all authors are employed by a commercial entity with a financial interest in the results of the study.

Registration of Clinical Trials. All clinical trials must be registered in a World Health organization-approved Clinical Trial registry prior to enrollment of the first subject. The registry name and registration number should be included on the title page. Reports of unregistered trials will be returned to authors without review. Publication of the results of a trial that was initiated prior to the ICMJE requirement for trial registration will be considered by the editors on a case-by-case basis.

Journal Style

All aspects of the manuscript, including the formatting of tables, illustrations, and references and grammar, punctuation, usage, and scientific writing style, should be prepared according to the most current *AMA Manual of Style* (http://www.amamanualofstyle.com). [1]

Author Listing. All authors' names should be listed in their entirety, and should include institutional/professional affiliations and degrees held.

Titles. *Pediatrics* generally follows the guidelines of the AMA Manual of Style for titles (http://www.amamanualofstyle.com). Titles should be concise and informative, containing the key topics of the work. Declarative sentences are discouraged as they tend to overemphasize a conclusion, as are questions, which are more appropriate for editorials and commentaries. Subtitles, if used, should expand on the title; however, the title should be able to stand on its own. It is appropriate to include the study design ("Randomized Controlled Trial"; "Prospective Cohort Study", etc.) in subtitles. The location of a study should be included only when the results are unique to that location and not generalizable. Abbreviations and acronyms should be avoided. The full title will appear on the article, the inside table of contents, and in MEDLINE. Full titles are limited to 97 characters, including spaces. Short titles must be provided as well and are limited to 55 characters, including spaces. Short titles may appear on the cover of the journal as space permits in any given issue.

Abbreviations. On the title page, authors should provide an alphabetically ordered list of abbreviations used in the manuscript and what they stand for. Unusual abbreviations should be avoided. All terms to be abbreviated in the text should be spelled out at first mention, followed by the abbreviation in parentheses. The abbreviation may appear in the text thereafter. Abbreviations may be used in the abstract if they occur 3 or more times in the abstract. Abbreviations should be avoided in tables and figures; if used they should be redefined in footnotes.

Key Words. Authors should provide key words on the title page, using Medical Subject Headings (MeSH) terms as a guide. Visit: *http://www.nlm.nih.gov/mesh/meshhome.html*

Units of Measure. Like many US-based journals, *Pediatrics* uses a combination of Système International (SI)[2,3] and conventional units. Please see the *AMA Manual of Style* for details.

Proprietary Products. Authors should use nonproprietary names of drugs or devices unless mention of a trade name is pertinent to the discussion. If a proprietary product is cited, the name and location of the manufacturer must also be included.

References. Authors are responsible for the accuracy of references. Citations should be numbered in the order in which they appear in the text. Reference style should follow that of the *AMA Manual of Style,* current edition. Abbreviated journal names should reflect the style of Index Medicus. Visit: *http://www.nlm.nih.gov/tsd/serials/lji.html*

Authoring Groups: If you choose to include an organization, committee, team, or any other group as part of your author list, you must include the names of the individuals as part of the Acknowledgments section of your manuscript. This section should appear after the main text prior to your References section. The terms "for" or "on behalf of" must also be used when referencing the authoring group in the by-line.

Manuscript Preparation

All submissions must adhere to the following format:
□ Times New Roman font, size 12
□ Title Page, Contributor's Statement Page, Abstract, Acknowledgments, and References should be **single-spaced**
□ Main Body Text should be **double-spaced**
□ Main Submission Document as Microsoft Word or RTF file (no PDFs)
□ Do **not** include page headers, footers, or line numbers

Refer to the "Article Types" section for specific guidelines on preparing a manuscript in each category. Note in particular the requirements regarding abstracts for different categories of article.

Title Page

The "title page" should be the first pages of your main document, and depending on the individual needs of a paper may encompass more than one page.

Title pages for all submissions **must** include the following:

1) Title (97 characters [including spaces] or fewer)
2) Full names for all authors, including degrees, and institutional/professional affiliations.
3) Contact information for the Corresponding Author (including: name, address, telephone, and e-mail).
4) A short title (55 characters [including spaces] or fewer). Please note: the short title may be used on the cover of the print edition.
5) Define all nonstandard abbreviations used 3 or more times in the text, in alphabetical order.
6) Key words. All manuscripts must include at least one key word.
7) Funding source. Research or project support, including internal funding, should be listed here; if the project was done with no specific support, please note that here. Technical and other assistance should be identified in Acknowledgments
8) Financial Disclosure Statement for all authors. Disclose any financial relationships that could be broadly relevant to the work. If none, say so.
9) Conflict of Interest Statement for all authors. If none, say so.
10) If applicable, Clinical Trial registry name and registration number
11) For regular article submissions, include the "What's Known on This Subject; What This Study Adds" (see below under article type for description). This is not needed for any other article type.

If a title page does not include all of the above items, the submission may be returned to the authors for completion.

[Sample Title Page]

Title of Manuscript [97 characters maximum, including spaces]

Alice Author[1], MD, Clarence CoAuthor[1,2], MD, PhD, Ann Analyst, MPH, on behalf of Authoring Group A

Affiliations: [1]Children's Hospital, Chicago, Il**;** [2]University of Chicago, Chicago, Il

Address correspondence to: Alice Author, Department of Pediatrics, Children's Hospital, 1234 Main Street, Chicago Il, 60641, [aauthor@example.com], 773-900-9000.

Short title: Short running title for Manuscript [55 characters maximum, including spaces]

Abbreviations: Hgb – hemoglobin; SES – socioeconomic status

Key Words: iron deficiency, anemia, infant, adult, developmental origins of health and Disease

Funding Source: All phases of this study were supported by an NIH grant, ######.
[or] No funding was secured for this study.

Financial Disclosure: Clarence CoAuthor has example disclosure. The remaining authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: Ann Analyst has example conflict. Clarence CoAuthor has other example conflict. The other authors have no conflicts of interest to disclose.

Clinical Trial Registration: (Registry name and registration number if any)
[for Regular Articles only:]

What's Known on This Subject
Max 40 words; in paragraph style (not bulleted lists)

What This Study Adds
Max 40 words; in paragraph style (not bulleted lists)

Clinical Trials

A study is considered a clinical trial if it prospectively assigns human subjects (whether randomized or not) to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. If authors report the results of a clinical trial, they must affirm that the study has been registered at www.clinicaltrials.gov or another WHO-approved national or international registry prior to the enrollment of the first subject. Information on requirements and appropriate registries is available at http://www.icmje.org/. The trial registration number must be listed on the title page, and at the end of the abstract. Authors are required to complete the CONSORT Form and submit it with their manuscript. In our submission system, this form appears under "Instructions and Forms" and can be reached at: http://mc.manuscriptcentral.com/societyimages/pediatrics/Consort%20Form.pdf.

Reuse of Data Sets

If a manuscript uses the same or similar data contained in previously published articles, the authors must state this in the initial letter of submission and provide citations to the related or possibly duplicative materials.

Contributors' Statement Page

All submissions must contain a Contributors' Statement Page, directly following the Title Page. Manuscripts lacking this page will be returned to the authors for correction.

All persons designated as authors should qualify for authorship (see above), and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. The Contributor's Statement Page should list the authors in order, and for each, specify the contribution(s) made by that individual. **Follow the required format** shown in this example when creating your Contributors' Statement Page:

Contributor's Statement:

George X. Smith: Dr. Smith conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted.
Roseanne Z. Jones, Allan Smithee, and Bill Weber: Drs. Jones, Smithee, and Weber carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted.
Tucker R. Green: Ms. Green designed the data collection instruments, and coordinated and supervised data collection at two of the four sites, critically reviewed the manuscript, and approved the final manuscript as submitted.

Note: Contributors who do not meet the criteria for authorship (such as persons who helped recruit patients for the study, or professional editors) should be listed in an Acknowledgments section placed after the manuscript's conclusion and before the References section. Because readers may infer their endorsement of the data and conclusions, these persons must give written permission to be acknowledged.

Word Count (Article Length)

To determine article length, count the body of the manuscript (from the start of the Introduction to the end of the Conclusion). The title page, contributor's statement page, abstract, acknowledgments, references, figures, tables, and multimedia are not included.

Article Types

Regular Article

Abstract length: 250 words or fewer (structured, as noted below)
Article length: 3,000 words or fewer

Regular Articles are original research contributions that aim to inform clinical practice or the understanding of a disease process. Regular Articles include but are not limited to clinical trials, interventional studies, cohort studies, case-control studies, epidemiologic assessments, and surveys. Components of a Regular Article include:

□ **What's Known on This Subject; What This Study Adds**
These brief summaries are each limited to 40 words. Please use precise and accurate language in paragraph form (i.e., *not bullet points*). For manuscripts accepted as Regular Articles, these summaries will become a highly visible part of your published paper, with prominence on the first page. Moreover, these summaries will be highlighted and presented in other areas of the journal, namely *Pediatrics Digest*. It is therefore paramount that you use language of the same caliber as the rest of your paper.

□ **Structured Abstract (four paragraphs with headings in boldface type)**
The abstract should consist of: Background (or Objectives, or Background and Objectives), Methods, Results, and Conclusions. The Objective should clearly state the hypothesis; Methods, inclusion criteria and study design; Results, the outcome of the study; and Conclusions, the outcome in relation to the hypothesis and possible directions of future study.

□ **Body of Article**
For the body of your article, follow this general outline:

- **Introduction**

A 1- to 2-paragraph introduction outlining the wider context that generated the study and the hypothesis.

- **Patients and Methods**

This section should detail inclusion criteria and study design to ensure reproducibility of the research. All studies that involve human subjects must be approved or deemed exempt by an official institutional review board; this should be noted here.

- **Results**

This section should give specific answers to the aims or questions stated in the introduction. The order of presentation of results should parallel the order of the methods section.

- **Discussion**

The section should highlight antecedent literature on the topic and how the current study changes the understanding of a disease process or clinical situation, and should include a section on the limitations of the present study.

- **Conclusion**

A brief concluding paragraph presenting the implications of the study results and possible new research directions on the subject.
General submission instructions (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) apply to Regular Articles.

Case Report

Abstract length: 250 words or less (unstructured: no headings, run in a single paragraph)
Article length: 1,600 words or less
Author limit: Seven (7) authors or less

Case Reports highlight unique presentations or aspects of disease processes that may expand the differential diagnosis and improve patient care. In general, case reports will include 10 cases or fewer. For a manuscript to be considered a Case Report, it must meet at least one of the following 3 criteria:
1) Challenge an existing clinical or pathophysiologic paradigm, and/or
2) Provide a starting point for novel hypothesis-testing clinical research, and/or
3) Offer a clinical "lesson" that may allow pediatric colleagues to provide improved care.

Case Reports should consist of an unstructured abstract that summarizes the case(s), a brief introduction (recommended length, 1-2 paragraphs), a section that details patient presentation, initial diagnosis and outcome, as well as a discussion that includes a brief review of the relevant literature and describes how this case brings new understanding to the disease process.

The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) also apply to Case Reports.

Commentary

Abstract length: no abstract
Article length: 400 to 800 words
Commentaries are opinion pieces consisting of a main point and supporting discussion. These contributions usually pertain to and are published concurrently with a specific article; the commentary serves to launch a broader discussion of a topic. Commentaries may address general issues or controversies in the field of pediatrics.

While the vast majority of commentaries are solicited, we do accept unsolicited commentaries. However, unsolicited commentaries will go through the same peer-review process as other papers, and acceptance rates are low. Responses to published articles should be submitted as eLetters (see below).

The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements, also apply to Commentaries).

Ethics Rounds

Ethics Rounds present discussions of cases that illustrate ethical dilemmas in patient care, research, or administration. Authors who have a case that raises ethical issues and who want to submit a paper for Ethics Rounds should email Assistant Editor John Lantos (jlantos@cmh.edu). The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements, also apply to Ethics Rounds).

Monthly Feature

Abstract length: no abstract
Article length: 1,200 words or less

The "Monthly Feature" column offers an opportunity to gain insight into aspects of our field: past, present, and future. Alternating monthly, the column will provide ongoing updates from three standing groups: (1) Global Health; (2) the Council on Medical Student Education in Pediatrics (COMSEP); and (3) the Historical Archives Advisory Committee for the AAP.

While many of the Monthly Features are invited, any queries or proposals should be directed to the editors of their respective columns: Jay Berkelhamer, MD (jberkelhamer@aap.net) for Global Health; Susan Bannister, MD (Susan.Bannister@albertahealthservices.ca) for COMSEP; and Jeffrey Baker, MD (Baker009@mc.duke.edu) for the AAP Historical Archives Advisory Committee.

The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) also apply to Monthly Features.

Pediatrics Perspectives

Abstract length: no abstract
Article length: 1,200 words max
Author limit: Three (3) authors or less

Pediatrics Perspectives are unsolicited commentaries that focus on issues of policy, public health, or other research and clinical topics related to infant, child, and/or adolescent health. These articles should be 1200 words maximum, be written by no more than three authors and have no more than 7 references.
The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) also apply to Pediatrics Perspectives.

Quality Report

Abstract: 250 words or less (structured: see Regular Articles)
Article: 3,000 words or less
Supplemental content: appropriate for figures, tables, multimedia, measurement tools

Quality Reports are intended to add to our understanding of how to improve quality in clinical settings in which pediatrics is practiced. Reports should provide descriptions of the change process, whether successful or unsuccessful, and include insights regarding why planned interventions did or did not lead to improvement. Descriptions of clinical trials to assess whether an intervention is effective or the development and testing of improvement-related tools for validity and reliability would be better suited as a Regular Article. However, pilot projects of interventions to improve the quality of care may be acceptable if there are important lessons that will serve as the basis for future studies. If you are uncertain whether your manuscript is appropriate as a Quality Report, email Interim Deputy Editor Alex Kemper, MD, MPH, MS (alex.kemper@duke.edu).

Authors are expected to generally follow the Standards for Quality Improvement Reporting Excellence (SQUIRE) Guidelines for reporting their quality improvement projects. These guidelines are described in detail on the SQUIRE website at www.squire-statement.org. Authors should note that the basic structure of a quality report should mirror the rest of the journal, using the IMRaD

(Introduction, Methods, Results, Discussion) format. The SQUIRE guidelines suggest specific areas that need to be addressed in each section, with recognition that every report will have different areas of emphasis.

The following list is a very brief description of the sections of a Quality Report; authors should refer to the full SQUIRE report at www.squire-statement.org.

□ **Introduction:** ***Why did you start?***
Summarizes background, local problem and local setting, and specific aim(s) of project.

□ **Methods:** ***What did you do?***
Describes ethical aspects, contextual issues, the intervention itself, implementation and evaluation plan, analysis.

□ **Results:** ***What did you find?***
Describes the actual course of the intervention, changes in process and outcomes, degree of success, problems and failures, lessons learned.

□ **Discussion:** ***What do the findings mean?***
Summarizes findings and considers factors that may have affected the outcome; includes interpretation of findings, conclusions, and next steps.
The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) also apply to Quality Reports.

Review Article

Abstract length: 250 words or less (structured or unstructured, depending on review type)
Article length: 4,000 words or less

Review Articles combine and/or summarize data from the knowledge base of a topic. Preference is given to systematic reviews and meta-analyses of clearly stated questions over traditional narrative reviews of a topic. Both types of review require an abstract; the abstract of a narrative review may be unstructured (no headings, run in a single paragraph). **See below for abstracts of systematic reviews and meta-analyses.**

The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) also apply to Review Articles.

Systematic Reviews and Meta-Analyses

Reports of systematic reviews and meta-analyses should use the PRISMA statement (http://www.prisma-statement.org/) as a guide, and include a completed PRISMA checklist and flow diagram to accompany the main text. Blank templates of the checklist and flow diagram can be downloaded from the PRISMA Web site (http://www.prisma-statement.org/statement.htm).
Structured abstracts for systematic reviews are recommended. Headings should include: Context, Objective, Data Sources, Study Selection, Data Extraction, Results, and Conclusions (see Iverson et al[1][pp22-23]).

Special Article

Abstract length: 250 words or less (unstructured: no headings, run in a single paragraph)
Article length: 4,000 words or less

Special Articles reflect topics or issues of relevance to pediatric health care that do not conform to a traditional study format. Special Articles may address broad social and ethical issues, scientific methodology, or other scholarly topics, and may include reports from consensus committees and working groups. These articles should not include specific guidelines or recommendations for practice. Guidelines and recommendations from groups outside of the AAP must be approved through the AAP and may be published at the discretion of the AAP in the Academy's dedicated section of the journal (see below). Special Articles may be submitted without an abstract (enter "N/A") in the abstract section of the online submission page), but the Medline entry will not have an abstract in that case.

The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) apply to Special Articles.

State-of-the-Art Review Article

Abstract length: 250 words or less (unstructured: no headings, run in a single paragraph)
Article length: 4,000 words or less

State-of-the-Art Review Articles provide a comprehensive and scholarly overview of an important clinical subject with a principle focus on developments in the past 5 years. State-of-the-Art Articles are usually invited. If you are interested in submitting a State-of-the-Art Review, please email Associate Editor Dr. Phyllis Dennery (dennery@email.chop.edu) and copy Editorial Associate Martha Andreas (martha.andreas@med.uvm.edu).

The general instructions regarding submission (including cover letter, title page requirements, contributor's statement page, journal style guidance, and conflict of interest statements) also apply to State-of-the-Art Reviews.

"From the American Academy of Pediatrics" [AAP use only]

The editorial process and manuscript selection for publication in *Pediatrics* are separate from the processes and materials that are produced or endorsed by the AAP. These materials are published in print and online in a visually distinct section of the journal. AAP Clinical Practice Guidelines, Policy Statements, Clinical Reports and other AAP-produced or endorsed materials that are intended to help guide practice are highly valued by membership, and are published in this section of the journal at the sole discretion of the AAP. Content produced or endorsed by the AAP is reviewed and approved outside of the *Pediatrics* editorial process.

Do not select an AAP Clinical Report, AAP Policy Statement, or other AAP article type for your submission. These are reserved for internal AAP use only.

Figures, Tables, and Multimedia

Figures

Authors should number figures in the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure should be accompanied by a legend that does not exceed 50 words. Abbreviations previously expanded in the text are acceptable. If a figure is reproduced from another source, authors are required to obtain permission from the copyright holder, and proof of permission must be uploaded at the time of submission.

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***Pediatrics* cannot accept Excel or PowerPoint files for any part of your submission.**

Tables

Tables should be numbered in the order in which they are cited in the text and include appropriate headers. Tables should not reiterate information presented in the Results section, but rather should provide clear and concise data that further illustrate the main point. Tabular data should directly relate to the hypothesis. Table formatting should follow the most current edition of the *AMA Manual of Style.*

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Presentation of Numbers and Statistics

☐ Results in the abstract and the paper generally should include estimates of effect size and 95% confidence intervals, not just P- values or statements that a difference was statistically significant.

☐ Statistical methods for obtaining all P-values should be provided

☐ Units of independent variables must be provided in tables and results sections if regression coefficients are provided

☐ Authors should avoid expressing effect sizes in the form of highly derived statistics.

Equations should be typed exactly as they are to appear in the final manuscript.
The following table, adapted from the guidelines for authors for the *Annals of Internal Medicine* by editors of *Medical Decision Making*, shows how to present certain percentages and some statistical measures:

Percentages Report percentages to one decimal place (i.e., xx.x%) when sample size is >=200. To avoid the appearance of a level of precision that is not present with small samples, do not use decimal places (i.e., xx%, not xx.x%) when sample size is < 200.

Error measures Report confidence intervals, rather than standard errors, when possible. Use "mean (errormeasures)" rather than "mean ± error measure" notation.

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Authors may wish to include additional information as part of their article for inclusion in the online edition of *Pediatrics*. References to any online supplemental information must appear in the main article. Such supplemental information can include but are not limited to additional tables, figures, videos, audio files, slide shows, data sets (including qualitative data), and online appendices. Authors are responsible for clearly labeling supplemental information and are accountable for its accuracy. *Supplemental information will be peer reviewed, but not professionally copyedited.*

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