Neonatal nutrition research – what do we need to know?

Nutrition in fetal life and early infancy influences long-term health, making it particularly important that nutrition is optimised at these early stages. Research needs to address all aspects of nutritional support: what and how much babies need, how and when to provide it, how to nurture the gut to enable nutrition and growth and how to ensure that all high-risk babies receive the best evidence-based nutritional care.

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Key points

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1. Significant improvements in research infrastructure have made it easier to perform neonatal nutrition research.
2. There is a growing body of skilled professionals that are keen to develop clinical trials and recruit babies to multicentre trials.
3. Questions remain about what, when and how much to feed, as well as the use of probiotics and lactoferrin.
4. Clinical and academic networks must work with families to ensure that opportunities to advance clinical care through research are fully embraced.

Nutrition is fundamental to life. The recognition that nutrition and growth in fetal life and early infancy influences long-term health makes it particularly important that nutrition is optimised at these early stages. Preterm infants are challenged by immature gut and metabolic function, and balancing requirements with tolerance requires detailed knowledge and skill. Managing nutrition within the context of a busy NICU is not easy. Research needs to address all aspects of nutritional support: what and how much babies need, how and when to provide it, how to nurture the gut to enable nutrition and growth and how to ensure that all high-risk babies receive the best evidence-based nutritional care, both while in hospital and on discharge.

Research infrastructure

Recent years have seen significant changes to research infrastructure in the UK at national, regional and local levels, which have helped both improve capacity and create more coordinated and structured research networks. One such infrastructure change was the establishment of the National Institute for Health Research (NIHR) in 2006[1]. This is a large, multifaceted organisation funded by the Department of Health. Essentially the research arm of the NHS, it aims to support outstanding individuals, facilities and leading-edge research focused on the needs of patients and the public. In particular, it has increased the volume of applied health research, with an emphasis on the translation of basic science into clinical practice. The NIHR infrastructure consists of a national Clinical Research Network and local clinical research facilities, centres and units. The NIHR Clinical Research Network is made up of several different national research networks of which six are 'topic specific', including the Medicines for Children Research Network (MCRN). The specific aim of the MCRN is to: "Improve the coordination, speed and quality of randomised controlled trials (RCTs) and other well designed studies of medicines for children and adolescents, including those for prevention, diagnosis and treatment". In addition, the MCRN also coordinates the NIHR Paediatric (Non-Medicines) Specialty Group. Within the MCRN, a national Neonatal Network has been established to aid large-scale neonatal studies. In the context of neonatal nutrition research, this is important as nutritional studies are increasingly powered on substantive outcome measures, such as mortality, necrotising enterocolitis (NEC), late onset infection and neurodevelopment, which require large numbers of extremely preterm infants. Collaboration between networks to aid recruitment of, and large data collection on, large numbers of preterm infants is therefore essential for these studies.

The MCRN also comprises 15 different Clinical Studies Groups (CSGs), which cover specific research areas and aim to provide an overview of the current portfolio of studies, as well as providing opinions or advice to potential or upcoming studies. The MCRN Neonatal CSG, provides oversight of all current national neonatal portfolio studies, with access to information on study aims, current recruitment and recruitment targets. This is important, as having an overview of the national neonatal research portfolio allows the CSG to advise on areas

Trial name	Design	Patient group	Intervention	Primary outcome	Total study number	Current status	Funding source	Chief investigator	Clinical trials unit	MCRN status
ADEPT	RCT	<35 weeks, IUGR	Early vs late enteral feeds	Time to full enteral feeds	404	Published	AMR	Alison Leaf	NPEU	Adopted
PiPS	RCT	<31 weeks, <48h	Probiotic vs placebo	NEC (Bell Stage 2 or 3) and death, sepsis (>72 hours after birth) and death	Target 1,300	Recruiting	NIHR HTA	Kate Costeloe	NPEU	Adopted
NEON	RCT	<31 weeks, <12h	High or low dose AA, started within 24h; SMOF vs intralipid	Non-adipose body mass on MRI; intra-hepatocellular lipid content using MRS	160	Data analysis	EME	Sabita Uttaya	CTEU Royal Brompton & Harefield NHSFT	Adopted
SCAMP	RCT	<29 weeks, <1,200g, <72h	Standard concentrated vs maximal PN concentration	Rate of head growth at 28 days	150	Recruiting	Bliss	Colin Morgan	Liverpool Women's NHSFT	Adopted
ELFIN	RCT	<32 weeks	Prophylactic enteral supplementation with bovine lactoferrin vs placebo	Late-onset invasive infection	Target 2,200	Due to start April 2013	NIHR HTA	William McGuire	NPEU	Adopted on NIHR portfolio
SIFT	RCT	<32 weeks or <1,500g	Slow vs fast milk feeds increase	Survival without moderate or severe disability at two years	Target 2,500	Due to start March 2013	NIHR HTA	Jon Dorling	NPEU	Adopted on NIHR portfolio

TABLE 1 Summary of recent, current and imminent UK trials of nutrition and feeding in the UK.
Key: RCT = randomised controlled trial, IUGR = intrauterine growth restricted, AA = amino acid, SMOF = soybean oil, medium-chain triglycerides, olive oil and fish oil, PN = parenteral nutrition, NEC = necrotising enterocolitis, MRI = magnetic resonance imaging, MRS = magnetic resonance spectroscopy, AMR = Action Medical Research, NIHR = National Institute of Health Research, HTA = Health Technology Assessment, EME = Efficacy and Mechanism Evaluation Programme, NPEU = National Perinatal Epidemiology Unit, MRCN = Medicines for Children Research Network, CTEU = Clinical Trials and Evaluation Unit, NHSFT = NHS Foundation Trust.

requiring more attention, or areas where certain study populations might become 'oversubscribed'. Again in the context of nutritional studies that can require large numbers, this oversight can help direct efforts accordingly or ensure trials are timed to start when others looking at a similar patient population are due to finish (**TABLE 1**).

In addition, there are 24 specialty groups within the NIHR Comprehensive Clinical Research Network, one of which is the Paediatric (Non-Medicines) Specialty Group. The remit of this group is to support a national portfolio of research studies in paediatrics, except those research studies that involve medicines. The Paediatrics (Non-Medicines) Specialty Group works very closely with the MCRN to ensure that there is a high quality research infrastructure in the NHS to support research involving neonates, infants, children and young people.

At a more local level, the NIHR also funds 11 Biomedical Research Centres (BRCs) and 20 Biomedical Research Units (BRUs). BRCs have substantial portfolios of research in one or several research areas, and promote innovation and translate research in biomedicine into NHS practice. BRUs have a similar remit but are focused on specific research areas with high disease burdens or clinical need. There are currently two BRUs (Bristol and Leicester) and one BRC (Southampton) that focus specifically on nutrition. The NIHR also funds (or co-funds) 18 Clinical Research Facilities for Experimental Medicine, which aim to speed up the translation of scientific advances to benefit patients.

At a more specialist level, there is also the Neonatal Nutrition Network (N3, www.nicunutrition.com), a national group of health professionals with an interest in improving the outcome of sick and preterm infants by optimising feeding and nutrition. This has informal links with the Royal College of Paediatrics and Child Health (RCPCH), the British Association of Perinatal Medicine (BAPM) and the British Society of Paediatric Gastroenterology Hepatology and Nutrition (BSPGHAN) and is also associated with the Neonatal CSG of the MCRN. In addition, the National Perinatal Epidemiology Unit (NPEU, www.npeu.ox.ac.uk) undertakes a broad range of clinical research aimed at producing methodologically rigorous research evidence to improve the care provided to women and their families during pregnancy, childbirth, the newborn period and early childhood, as well as promoting the effective use of resources by perinatal health services. The NPEU's research is funded from a variety of

sources; the Department of Health Policy Research Programme (PRP) provides funding for an extensive and broad 'Programme of Work' covering a five-year period and the multicentre clinical trials are all grant funded, predominantly by NIHR funding streams.

What nutrients and how much?

An important first step in reviewing the direction of future neonatal nutrition research is to consider the objectives. A goal in the nutritional care of preterm infants is to try and maintain growth comparable to that which would be seen *in utero* at equivalent gestations[2]. This growth should be appropriate both quantitatively, with appropriate gains in weight, length and head circumference, and qualitatively, with infants achieving an appropriate body composition in terms of the proportions of fat and lean tissue. The quantity and quality of nutrition provided will therefore need to be correct in order to achieve this. Guidance exists regarding nutritional targets for extremely preterm infants; the requirements of term infants are well established[3,4]. However, there is little information regarding the nutritional needs of infants born in the 'moderate-to-late' preterm group (32-37 weeks) and there is a need to establish the nutritional needs and optimum feeding strategies for these infants. This is particularly pertinent given the growing body of evidence that these infants have suboptimal respiratory and neurodevelopmental outcomes, suggesting that the adverse outcomes associated with prematurity are on a spectrum from extreme preterm birth through to term[5-7].

While recommended nutritional targets exist for extremely preterm infants, there is good evidence that preterm infants as a group often fail to achieve these targets[8,9] and this has led to an interest in strategies to address shortfalls. These range from enhanced or concentrated parenteral nutrition (PN), through to clinical interventions aimed at standardising and optimising nutritional care. Current trials include the SCAMP study (Standardised, Concentrated, Additional Macronutrients, Parenteral nutrition)[10] and the NEON study (Nutritional Evaluation and Optimisation in Neonates) – an optimised amino acid and lipid regimen in PN[11] (**TABLE 1**). Such strategies offer promise, and improvements in nutritional care have meant that clinicians are now closer to consistently meeting nutritional targets and achieving optimum growth[12]. However, more work is required in order to establish efficacy and safety, as the use of higher amounts of nutrition to improve growth raises the issue of possible maximum safe limits for some nutrients, particularly protein[13]. Furthermore, the ability to get closer to recommended targets, combined with growing evidence regarding growth and later outcomes such as neurodevelopment[14,15] and the risk of cardiovascular disease[16,17], means there may be a need to begin to reconsider the validity of those original recommendations, which were essentially consensus opinion based on a review of scientific evidence available at the time.

FIGURE 1 The distribution of centres recruiting preterm infants for the Abnormal Doppler Enteral Prescription Trial (ADEPT).

Research outcome measures

There is increasing interest regarding the most appropriate outcome measures in nutrition research. Given that nutritional care aims to achieve body size and composition comparable to a full term infant, good measures of growth and body composition are vital. Weight, length and head circumference measurements should be part of routine care and provide readily available outcome data. However, in the context of research it is vital that these 'routine' measures are carried out in a standardised manner – protocols can help achieve this. The body composition of preterm infants at term equivalent age is currently different to infants born full term, so there is a need to consider body composition carefully[18]. This is more difficult to measure, and there is currently no 'gold standard' method for use in studies. Methods range from simple but relatively inaccurate techniques such as skinfold thickness or bioelectrical impedance, through to dual X-ray absorptiometry (DXA), magnetic resonance imaging (MRI) and air displacement plethysmography (ADP), which have better validity but are more cumbersome and expensive[19]. More research is needed in this area in order to establish the most appropriate techniques, together with reference data sets.

In relation to this, a recent systematic review looking at PN in preterm infants highlighted variability in growth outcomes reported by neonatal nutritional studies, with disparate time points and choices of measurements[20]. Given that the preterm population is limited in size, it is vital that there is more consistency in the outcomes measured in neonatal studies that would facilitate prospective meta-analyses to answer important clinical questions. This could involve the COMET (Core Outcome Measures in Effectiveness Trials) initiative which works towards bringing together researchers interested in the development and application of agreed standardised sets of outcome measures[21].

While measures of growth and composition are clearly important, ultimately the main outcomes of interest will be those impacting on later life or associated with a significant healthcare burden. Several studies have shown a clear link between early nutrition and growth and neurodevelopmental outcomes at 18 months to two years of age, and such outcomes are clearly an important measure of the impact of any nutritional intervention in the neonatal period[14,15]. This presents a challenge, as more resources are needed for follow-up and the number of infants required to provide sufficient power to detect statistically significant and clinically important differences in neurodevelopmental outcomes are in the order of thousands. There is therefore a clear requirement to work within the networks described above in order to run successful multicentre nutritional trials in the preterm population. In addition, the need to follow-up such large numbers of infants in order to obtain these outcome measures requires a coordinated approach to ensure both completeness of follow-up and unnecessary repeat appointments.

When and how should we feed high-risk preterm infants?

Research questions such as when to start enteral feeds and how quickly to advance volumes might not seem exciting, however as these issues affect every preterm infant, even small differences can make a huge difference in terms of both clinical outcomes and use of resources.

When to start?

'ADEPT' – the Abnormal Doppler Enteral Prescription Trial (**TABLE 1**), was set up to answer a simple question: was it better to start enteral feeds early or late in preterm infants, born growth-restricted and with evidence of abnormal antenatal Doppler blood flow in the umbilical artery? The knowledge that these babies are at high-risk for NEC[22] had resulted in many neonatal units having policies to delay enteral feeding, however there was no good evidence to support this practice. Between 2006 and 2009, 404 infants of less than 35 weeks' gestation, were recruited in 53 hospitals in the UK and Ireland (**FIGURE 1**) and randomised to start enteral feeding on either day 2 or day 6 after birth. Increase of feeds was guided by an 'enteral prescription' which was included in the study protocol[23] and which allowed a slower rate of progression for the smallest and least mature infants, such that 'early feeding' babies would aim to achieve full feeds between day 10 and day 14 after birth and those in the 'late feeding' group between day 14 and day 18. The results showed that babies in the early feeding group achieved full enteral feeding significantly sooner than those in the late feeding group, with no difference in rates of NEC. Time to full feeds (sustained for 72 hours) and occurrence of any stage of NEC were the two primary outcomes. Other significant differences were a shorter duration of PN and high-dependency care, and a lower incidence of cholestasis in the early feeding group[24]. As well as providing useful answers to an important clinical question, ADEPT proved that there is enthusiasm and ability to conduct large and successful multicentre trials of neonatal feeding practice in the UK.

Systematic reviews with meta-analysis of combined data are a useful way in which to summarise best available evidence from clinical trials. The Cochrane Database of Systematic Reviews contains a number of reviews of relevance to preterm infant feeding and nutrition. Prior to ADEPT, 115 babies had been studied in three small RCTs of early (<4 days) compared to late (>4 days) introduction of feeding[25]. The conclusion was that there was no difference in weight gain or length of stay, and although no difference was seen in incidence of NEC, numbers were too small for this to be meaningful. This systematic review was updated in 2011, including early (and incomplete data) from ADEPT with the total number of cases increased to 600[26]. The conclusion states that there is no evidence that delaying feeds reduces the risk of NEC, however further data would be required to improve the precision of estimates on outcomes.

How fast to increase?

Another 'simple' question frequently asked is: how fast should feeds be increased? A systematic review of this subject was updated in 2011[27]. Four studies were included, with a total of 496 infants; 'slow' increase was defined as 15-20mL/kg/day and 'fast' as 30-35mL/kg/day. Meta-analysis showed that infants fed slowly took significantly longer to reach full enteral feeds and to regain birthweight, but there was no difference in rate of NEC (relative risk 0.91, 95% confidence interval 0.47-1.75) or all cause mortality (relative risk 1.43, 95% confidence interval 0.78-2.61). This is now going to be the topic of a large multicentre RCT – the Speed of Increasing Feeds Trial (SIFT)[28]. The trial aims to recruit 2,500 infants of less than 32 weeks' gestation and will be run by the NPEU Clinical Trials Unit (CTU). The primary outcome is survival without moderate or severe disability at 24 months of age corrected for prematurity (**TABLE 1**).

Trophic feeding

Another topic of interest, summarised in a systematic review, is trophic feeding or minimal enteral nutrition[29]. In this review there were nine trials, including 754 very low birthweight (VLBW) infants. Rather disappointingly, given the results of earlier physiological studies[30], there was no effect seen on feed tolerance or growth rates. Again no difference was seen in rates of NEC (relative risk 1.07, 95% confidence interval 0.67-1.70).

As can be seen from these systematic reviews, one reason that these simple questions are taken so seriously is because of the strong associations between enteral feeding and NEC. However, to date none of the trials and systematic reviews have shown a significant difference in NEC between intervention groups.

NEC remains one of the main challenges in establishing feeding/normal gut function in preterm infants. A thorough review of NEC[31] emphasised the importance of the intestinal microbiome, and the roles of inflammation and immune modulation in healthy adaptation of the immature gut. This is another area of exciting research in neonatal medicine, and two aspects are currently being addressed in the UK.

Optimising gut function

Probiotics

'Healthy bacteria' are crucial to normal intestinal function and it is well recognised that colonisation of the hospitalised preterm infant's gut is very different to the spectrum of organisms seen in a breastfed term infant. A systematic review and meta-analysis published in 2010[32], showed that administration of probiotic bacteria to preterm infants significantly reduced the rate of death and NEC with relative risks of 0.35 (95% confidence interval 0.23-0.55) and 0.42 (95% confidence interval 0.29-0.26) respectively. However detailed review of the included studies revealed that few VLBW and extremely preterm infants were included and few infants were receiving breast milk, thus interpretation and translation to contemporary UK neonatal populations is difficult. The Probiotics in Preterm babies Study (PiPS) hopes to address these limitations, as well as making detailed microbiological assessments of babies receiving probiotics (*Bifidobacterium breve* strain BBG) and population studies within participating centres. Again, NPEU CTU is running the trial and recruiting 1,300 babies of less than 31 weeks' gestation (**TABLE 1**).

Lactoferrin

Lactoferrin is a protein found in high concentration in colostrum and breast milk. It is an iron-binding glycoprotein and is an important component of the innate immune system. Intake is often low in preterm infants due to delay in establishing enteral feeding and there is evidence that supplementation may reduce the risk of infection, and along with the use of probiotics may also reduce the incidence of NEC[33]. A number of large-scale trials are being planned, including ELFIN in the UK (**TABLE 1**),

aiming to address the effect of enteral lactoferrin supplementation on these important outcomes in VLBW infants[34].

Strategies to implement change

Clinical trials and systematic reviews are important mechanisms for generating and summarising definitive evidence for effective clinical interventions. However, it is well recognised that adoption of evidence-based practice is often slow and incomplete. A further stream of research is now developing, with the aim of understanding how best to implement change and expedite best practice. As part of the Vermont Oxford Network Quality Improvement Collaborative (NIC/Q), Kuzma-O'Reilly and colleagues were the first to publish data showing improvements in nutritional care and outcomes through the application of 'potentially better practices'[35]. In Southampton, the sociological framework of 'normalisation process theory'[36,37] is currently used to assess and guide the process of introducing a complex nutritional intervention into the neonatal unit, as part of the Standardising Preterm Infant Nutrition study (SPIN).

Conclusion

In summary, neonatal nutrition research in the UK is in good shape. Recent years have seen a massive overhaul of research infrastructure, allowing improved communication, development of networks and access to training and financial support. There is a growing body of academic neonatologists keen to lead and develop clinical trials and a large number of neonatal doctors and nurses with skills, experience and commitment, willing to recruit babies to multicentre trials. Progress is being made, but there are still plenty of questions unanswered, and as survival of preterm infants improves, ever greater challenges arise of how best to meet the nutritional needs of these most vulnerable babies.

Clinical and academic networks are essential to optimise coordination and communication; however it is also vital to work in close partnership with parents. A greater number of trials will increase the likelihood of being approached to participate in one or more research study, and it is therefore essential that staff work closely with families to ensure that the opportunities to advance clinical care through research are fully understood and embraced by all.

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