

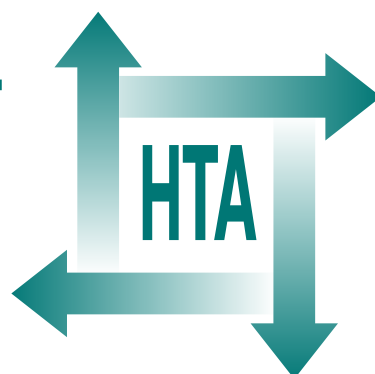
## **Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis**

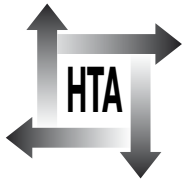
MJ Renfrew, D Craig, L Dyson,  
F McCormick, S Rice, SE King,  
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# Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis

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## Abstract

### Breastfeeding promotion for infants in neonatal units: a systematic review and economic analysis

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**Objectives:** To evaluate the effectiveness and cost-effectiveness of interventions that promote or inhibit breastfeeding or feeding with breastmilk for infants admitted to neonatal units, and to identify an agenda for future research.

**Data sources:** Electronic databases were searched (including MEDLINE and MEDLINE In-Process Citations, EMBASE, CINAHL, Maternity and Infant Care, PsycINFO, British Nursing Index and Archive, Health Management Information Consortium, Cochrane Central Register of Controlled Trials, Science Citation Index, Pascal, Latin American and Caribbean Health Sciences, MetaRegister of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment Database, National Research Register) from inception to February 2008. Advisors identified further published or unpublished material.

**Review methods:** All papers fulfilled eligibility criteria covering participants, interventions, study design and outcomes. Results from primary studies were assessed and summarised in a qualitative synthesis for each type of intervention and across types of intervention. To estimate long-term cost utility, a decision tree was developed to synthesise data on enhanced staff contact, breastmilk effectiveness, incidence of necrotising enterocolitis (NEC) and sepsis, resource use, survival and utilities.

**Results:** Forty-eight studies met the selection criteria for the effectiveness review, of which 65% (31/48) were RCTs, and 17% (8/48) were conducted in the UK. Seven were rated as good quality and 28 as moderate quality. No studies met the selection criteria for the health economics review. There is strong evidence that short periods of kangaroo skin-to-skin contact increased the duration of any breastfeeding for 1 month after

discharge [risk ratio (RR) 4.76, 95% confidence interval (CI) 1.19 to 19.10] and for more than 6 weeks (RR 1.95, 95% CI 1.03 to 3.70) among clinically stable infants in industrialised settings. There is strong evidence for the effectiveness of peer support at home (in Manila) for mothers of term, low birthweight infants on any breastfeeding up to 24 weeks (RR 2.18, 95% CI 1.45 to 3.29) and exclusive breastfeeding from birth to 6 months (RR 65.94, 95% CI 4.12 to 1055.70), and for the effectiveness of peer support in hospital and at home for mothers of infants in Special Care Baby Units on providing any breastmilk at 12 weeks [odds ratio (OR) 2.81, 95% CI 1.11 to 7.14;  $p = 0.01$ ]. There is more limited evidence for the effectiveness of skilled professional support in a US Neonatal Intensive Care Unit on infants receiving any breastmilk at discharge (OR 2.0, 95% CI 1.2 to 3.2,  $p = 0.004$ ). Multidisciplinary staff training may increase knowledge and can increase initiation rates and duration of breastfeeding, although evidence is limited. Lack of staff training is an important barrier to implementation of effective interventions. Baby Friendly accreditation of the associated maternity hospital results in improvements in several breastfeeding-related outcomes for infants in neonatal units. Limited evidence suggests that cup feeding (versus bottle feeding) may increase breastfeeding at discharge and reduce the frequency of oxygen desaturation. Breastmilk expression using simultaneous pumping with an electric pump has advantages in the first 2 weeks. Pharmaceutical galactagogues have little benefit among mothers who have recently given birth. Our economic analysis found that additional skilled professional support in hospital was more effective and less costly (due to reduced neonatal illness) than normal staff contact. Additional support ranged from 0.009 quality-adjusted life-years (QALYs) to 0.251 QALYs more beneficial

per infant and ranged from £66 to £586 cheaper per infant across the birthweight subpopulations. Donor milk would become cost-effective given improved mechanisms for its provision.

**Conclusions:** Despite the limitations of the evidence base, kangaroo skin-to-skin contact, peer support, simultaneous breastmilk pumping, multidisciplinary staff training and the Baby Friendly accreditation of the associated maternity hospital have been shown to be effective, and skilled support from trained staff in

hospital has been shown to be potentially cost-effective. All these point to future research priorities. Many of these interventions inter-relate: it is unlikely that specific clinical interventions will be effective if used alone. There is a need for national surveillance of feeding, health and cost outcomes for infants and mothers in neonatal units; to assist this goal, we propose consensus definitions of the initiation and duration of breastfeeding/ breastmilk feeding with specific reference to infants admitted to neonatal units and their mothers.



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## Glossary and list of abbreviations

### Glossary

**Acceptability curves** Cost-effectiveness acceptability curves show the probability that an intervention is more cost-effective than its comparator at different cost-effectiveness thresholds.

**Any or partial breastfeeding** Some breastfeeding plus water-based fluids, solids, milks or gruels.

**Appropriate for gestational age** An infant's birthweight that lies between the 10th and 90th centiles for gestational age at birth.

**Baby Friendly accreditation** The Baby Friendly Initiative accredits maternity and community health-care facilities and higher education institutions that have implemented best practice for breastfeeding and have passed an external assessment.

**Baby Friendly Initiative** A worldwide programme of the World Health Organization and UNICEF to encourage maternity hospitals to implement the Ten Steps to Successful Breastfeeding and to practise in accordance with the International Code of Marketing of Breastmilk Substitutes.

**Base-case model** A model that normally includes the best assumptions and data estimates in the analysis.

**Bolus feeding** A calculated amount of fluid, given intermittently depending on weight and gestational age.

**Breastfeeding counsellors** Women who have breastfed and completed an accredited training. In the UK these are run by volunteer organisations: the National Childbirth Trust; La

Leche League; the Breastfeeding Network; and the Association of Breastfeeding Mothers.

**Breastmilk substitute** Any fluid or food other than breastmilk that is used to feed infants. It may be used instead of, or as well as, breastmilk.

**Catch-up growth** A growth trajectory that crosses centile lines upwards or an improvement in the standard deviation score indicating reversion to the genetically determined body size.

**Chronological age** The age of the infant in weeks from the date of birth without correcting for prematurity.

**Comparator** The treatment with which the intervention in question is compared.

**Complementary food** Any food, whether manufactured or locally prepared, that is suitable as a complement to breastmilk or infant formula to satisfy the nutritional requirements of the infant.

**Composite milk** A combination of the fore- and hindmilk produced by lactating mothers.

**Corrected age** The age of the infant in weeks from the date of birth minus the number of weeks of prematurity.

**Cup feeding** A method of feeding in which the infant licks or sips breastmilk from a specially designed cup.

**Duration of breastfeeding** The period beyond the first nutritive breastfeed for which a baby continues to feed at the breast.

*continued*

**Enhanced staff contact** The provision of specially trained staff to advise and support mothers about milk expression and breastfeeding.

**Enteral feeding** The administration of any feed into the gastrointestinal tract.

**EQ-5D data** The preference measure of health states produced by the EuroQol Group, which contains five dimensions of health, where 1 is perfect health and 0 is death.

**Exclusive breastfeeding** Breastfeeding with no supplemental liquid or solid foods other than medications or vitamins.

**Finger feeding** A method of feeding in which a tube filled with, or attached to a container of, expressed breastmilk is attached to the caregiver's finger and inserted into the infant's mouth to enable ingestion of breastmilk.

**Foremilk** The low-fat, higher volume breastmilk obtained at the beginning of a breastfeed.

**Formula** Cow's or soy milk modified in line with *Codex Alimentarius* standards to provide the nutritional requirements of infants.

**Fortified feeds, fortifiers** Milk protein, vitamins and minerals that are added to breastmilk with the aim of meeting preterm infants' specific nutritional needs.

**Gavage feeds** The introduction of food into the stomach by means of a tube inserted through the mouth (orogastric) or the nose (nasogastric).

**Gestational age** The age in weeks and days of the fetus counted from the first day of the mother's last menstrual period.

**Galactagogue** Any substance (e.g. food, medicine) that aims to increase breastmilk production.

**Growth restricted** Describing infants who have experienced intrauterine growth restriction.

**Hand expression** The expression of milk from the breast by hand.

**Hindmilk** The high-fat breastmilk produced after the foremilk.

**Industrialised setting** A country or region whose economy is based on industry; generally located in the northern and western hemispheres (Natural Resources Defense Council). This level of economic development usually translates into a high income per capita and a high Human Development Index (HDI) for populations within that country or region.

**Initiation of breastfeeding** In the context of neonatal care settings, initiation of breastfeeding is defined as the mother putting the baby to the breast and the baby demonstrating nutritive sucking.

**Initiation of feeding with breastmilk** In the absence of agreed definitions, we suggest: 'In the context of neonatal care settings, initiation of feeding with breastmilk for the baby is defined as the baby receiving mother's or donor breastmilk by any method. For the mother, it is defined as any attempt to express breastmilk by any method.'

**Intention to treat** All participants are analysed by original allocated group including those who were lost to the study.

**International Code of Marketing of Breast Milk Substitutes** A code ratified by the World Health Assembly in 1981, and amended by its subsequent resolutions. It sets out the conditions under which breastmilk substitutes may be marketed to the public and health professionals. It has been adopted in whole or in part into the laws of several countries.

**Interquartile range** Shows the spread of the central 50% of a distribution.

**Kangaroo skin-to-skin contact** Ongoing skin-to-skin contact with the infant held between the mother's breasts in an upright position.

**Lactation consultant** An International Board Certified Lactation Consultant (IBCLC) is a health-care professional who specialises in the clinical management of breastfeeding. IBCLCs

are certified by the International Board of Lactation Consultant Examiners.

**Low birthweight infant** An infant with a birthweight of less than 2500 g.

**Medicaid** A scheme that provides medical benefits to groups of low-income people with no or inadequate medical insurance in the USA.

**Milk banking** A service that collects, screens, processes, stores and distributes breastmilk.

**Multiples** Infants born as a result of the multiple birth of more than two infants (i.e. triplets, quadruplets and more).

**Nasogastric** Describing the administration of feeds via gavage tube in the nose.

**Non-nutritive sucking/suckling** Sucking using a pacifier or other object, or at the breast without ingestion of breastmilk.

**Oral feeding** The administration of any feed into the oral cavity.

**Orogastric feeding** The administration of feeds via gavage tube in the mouth.

**Oxygen saturation** The percentage of circulating haemoglobin that is oxygenated.

**Parenteral feeding** The partial or total intravenous provision of fluid and nutrients when infants are unable to accept these by the gastrointestinal route.

**Peer support** Support offered by women, usually trained, who have breastfed and are from a similar socioeconomic, ethnic or cultural background to the client.

**Postconceptional age** The age in weeks and days of the infant from conception.

**Postrandomisation exclusions** Losses from the study after the point of randomised allocation.

**Post-term birth** A birth occurring after 42 completed weeks of gestational age.

**Preterm birth** A birth occurring before 37 completed weeks of gestational age.

**Preterm formula** Cow's or soy milk modified in line with *Codex Alimentarius* standards to provide the specific nutritional needs of preterm infants, principally those born before 32 weeks' gestation or weighing under 1500 g at birth.

**Preterm infant** An infant born before 37 weeks' completed gestation from the first day of the mother's last menstrual period.

**Respiratory support** Facilitation of the infant's gas exchange by continuous positive airways pressure or ventilation delivered through an endotracheal tube, face mask or nasal device.

**Small for gestational age** Describing an infant whose birthweight is less than the 10th centile for gestational age at birth.

**Spoon feeding** Feeding from a spoon.

**Stable infant** An infant whose vital functions, respiration and heart rate are not subject to rapid and unexpected worsening, nor dependent on continuous medical monitoring and support.

**Term birth** A birth occurring after 37 completed weeks and before 42 completed weeks of gestational age.

**Test weighing** Weighing of infants before and after intake of breastmilk.

**US Department of Agriculture's Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)** Health sector initiatives delivered at the local level as part of the national WIC Program targeting women of low incomes in the USA.

**Very low birthweight** Describing an infant with a birthweight of less than 1500 g.

## List of abbreviations

AGA	appropriate for gestational age	NICE	National Institute for Health and Clinical Excellence
B/A	before/after study	NICU	Neonatal Intensive Care Unit
BF (bf)	breastfeeding	NIDCAP	Newborn Individualised Developmental Care and Assessment Programme
BFI	Baby Friendly Initiative	NIPPV	nasal intermittent positive pressure ventilation
BW	bodyweight	NITB	no intention to breastfeed
C	control	non-RCT	non-randomised controlled trial
CA	chronological age	OMM	own mother's milk
CEMACH	Confidential Enquiry into Maternal and Child Health	OR	odds ratio
CHBS	Conventional Hospital Breastfeeding Support	PES	Parental Expectations Survey
CI	confidence interval	PRE	postrandomisation exclusion
CPAP	continuous positive airway pressure	PSA	probabilistic sensitivity analysis
EBM	expressed breastmilk	PSS-NICU	Parental Stressor Scale – NICU
FDA	Food and Drug Administration	QALY	quality-adjusted life year
GA	gestational age	RCT	randomised controlled trial
HDI	Human Development Index	RR	relative risk
HEED	Health Economic Evaluations Database	SAIB	Systematic Assessment of the Infant at the Breast (scale)
I	intervention	SCBU	Special Care Baby Unit
IBCLC	International Board Certified Lactation Consultant	SD	standard deviation
ICER	incremental cost-effectiveness ratio	SEM	standard error of the mean
IQR	interquartile range	SES	socioeconomic status
ITB	intention to breastfeed	SGA	small for gestational age
ITT	intention-to-treat	SSBC	Supplemented Structured Breastfeeding Counselling
KMC	kangaroo mother care	STS	skin-to-skin contact
LBW	low birthweight	TT	therapeutic touch
MTT	mimic therapeutic touch	UN	United Nations
NDI	neurodevelopmental impairment	VLBW	very low birthweight
NEC	necrotising enterocolitis	WHO	World Health Organization
NGT	nasogastric tube	WIC	(Program for) Women, Infants, and Children (US Department of Agriculture's Special Supplemental Nutrition Program)
NHS EED	NHS Economic Evaluation Database		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



## Executive summary

### Background

For preterm, growth-restricted and sick neonates, including those requiring surgery, the use of breastmilk substitutes is associated with increased short- and long-term adverse outcomes. These include mortality and serious morbidity in the infant and adverse health outcomes in the mother. The fragility of such infants, their changing nutritional and health needs, the increased difficulty in producing breastmilk experienced by preterm mothers, the anxiety that is inevitably provoked in mothers and family members, and the fact that health-care staff may not have the skills or the time needed, can make breastfeeding/breastmilk feeding a difficult process. A consequence of the recent improvement in survival rates at all gestations is the increasing numbers of infants in neonatal units with complex needs. Lack of feeding with breastmilk for these infants is an important and costly problem that, if addressed successfully, has the potential to contribute to addressing inequalities in health.

### Objectives

The primary aims of this systematic review and economic analysis were to evaluate the effectiveness and cost-effectiveness of interventions that promote or inhibit breastfeeding or feeding with breastmilk for infants admitted to neonatal units, and to identify an agenda for future research.

### Methods

#### Systematic review of effectiveness and health economics review

Electronic databases (including MEDLINE and MEDLINE In-Process Citations, EMBASE, CINAHL, Maternity and Infant Care, PsycINFO, British Nursing Index and Archive, Health Management Information Consortium, Cochrane Central Register of Controlled Trials, Science Citation Index, Pascal, Latin American and Caribbean Health Sciences, MetaRegister of Controlled Trials, Cochrane Database of Systematic

Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment Database, National Research Register) were searched using structured searches from inception to February 2008. References of retrieved papers were examined, and experts on the advisory group and clinical advisors were asked to identify further published or unpublished material.

#### Inclusion and exclusion criteria

##### Effectiveness review

Eligible studies had to fulfil all of the following:

- Participants: infants, or mothers of infants, who were admitted to neonatal units; and those linked to such infants and women, including fathers/partners, other family members or health professionals.
- Interventions: any type of intervention that addressed breastfeeding/feeding with breastmilk in neonatal units or following discharge.
- Outcomes: primary outcomes were measures of breastfeeding/breastmilk feeding. Secondary outcomes included clinical/health, process, psychosocial and cost-effectiveness outcomes. Studies that did not report a breastmilk or breastfeeding outcome were excluded.
- Study designs: randomised controlled trials (RCTs), randomised crossover studies, concurrent comparisons and before/after studies. Case studies and studies that did not evaluate an intervention were excluded.

##### Health economics review

Studies were eligible if they were full economic evaluations and were considered to be useful in answering the research question relating to cost-effectiveness.

##### Data extraction and validity assessment

Data were extracted and appraised for quality using structured tables relevant for each study design, based on CRD report 4, NICE guidance methodology and the Cochrane Handbook. Data extraction and quality assessment were independently checked by a second reviewer.

### Data synthesis

Results from primary studies were assessed and summarised in a qualitative synthesis for each type of intervention and across types of intervention. Relative risks for outcomes were estimated on an intention-to-treat (ITT) basis where appropriate; the ITT analysis was adjusted where possible for legitimate postrandomisation exclusions. Pooling of relative risks was not considered appropriate due to the heterogeneity of studies.

### Decision analysis

The objective of the model was to estimate the long-term cost utility of enhanced staff contact in promoting breastfeeding to mothers whose infants were admitted to neonatal units. A decision tree was developed to synthesise data on enhanced staff contact, breastmilk effectiveness, incidence of necrotising enterocolitis (NEC) and sepsis, resource use, survival and utilities. The structure of the model was determined by the evidence obtained during early stages of the effectiveness review and by the clinical studies identified in the additional modelling searches. It was finalised by means of a series of meetings with clinical advisors.

### Framing recommendations

To inform implications for policy and practice and recommendations for research, two additional approaches were used:

- Seven expert clinical informants from neonatal units in the UK and internationally identified key factors in introducing successful breastfeeding/breastmilk feeding-related change.
- Based on the findings of the study, the research team and advisory group members agreed implications for policy, practice and education and prioritised suggestions for future research studies.

## Results

### Health economics review

No studies met the selection criteria.

### Effectiveness review

A total of 48 studies met the selection criteria, of which 65% (31/48) were RCTs, and 17% (8/48) were conducted in the UK. Topics and numbers of studies identified were:

- increased mother and baby contact (12)
- interim feeding methods and related interventions (6)
- methods of expressing breastmilk (6)
- enhancing breastmilk production (7)
- supporting optimal nutritional intake from breastmilk (3)
- breastfeeding education and support (6)
- staff training (2)
- early hospital discharge with home support (2)
- organisation of care (4).

Studies were heterogeneous in terms of design, intervention, participants and outcomes measured. Seven were rated as good quality and 28 as moderate quality. Although the results should be viewed with some caution as a result, a useful evidence base has been identified.

*Increased mother and baby contact (nine RCTs, two before/after and one crossover study)* There is strong evidence that short periods of kangaroo skin-to-skin contact, of up to one hour at all visits, increased the duration of any breastfeeding up to 1 month after hospital discharge [risk ratio (RR) 4.76, 95% confidence interval (CI) 1.19 to 19.10] and for more than 6 weeks (RR 1.95, 95% CI 1.03 to 3.70) among clinically stable infants in industrialised settings, and daily contact improved health outcomes at 2 and 6 months in all settings.

*Interim feeding methods and related interventions (five RCTs, one crossover study)* The evidence for the use of cup feeding versus bottle feeding is limited, but it may increase breastfeeding at discharge and reduce the frequency of oxygen desaturation. Lack of staff training is an important confounder. There is no evidence to support the use of gavage feeding versus bottle feeding or the use of caregivers' fingers in place of pacifiers.

*Methods of expressing breastmilk (five RCTs, one crossover study)* Simultaneous pumping with an electric pump has advantages in the first two weeks. Once discharged home, the mother may also benefit from a hand-operated pump or hand expression, potentially increasing scope for more widespread provision by neonatal units within limited budgets.

*Enhancing breastmilk production (five RCTs, two crossover studies)* Pharmaceutical galactagogues seem to have little role to play among mothers who have recently given birth; there may be a role for these in later lactation for mothers whose milk production is not meeting their infant's

needs if used with supportive care. There is some evidence to support the use of relaxation-related interventions for mothers.

*Supporting optimal nutritional intake from breastmilk (two RCTs, one concurrent comparison)* Enhancing the composition of mother's own milk offers an apparently simple method for optimising protein and lipid intake. Good quality evidence of effectiveness is lacking.

*Breastfeeding education and support (three RCTs, three before/after studies)* There is strong evidence for the effectiveness of peer support at home (in Manila) for mothers of term, low birthweight infants on any breastfeeding up to 24 weeks (RR 2.18, 95% CI 1.45 to 3.29) and exclusive breastfeeding from birth to 6 months (RR 65.94, 95% CI 4.12 to 1055.70), and for the effectiveness of peer support in hospital and at home for mothers of infants in Special Care Baby Units on providing any breastmilk at 12 weeks [odds ratio (OR) 2.81, 95% CI 1.11 to 7.14;  $p = 0.01$ ]. There is more limited evidence for the effectiveness of skilled professional support in a US Neonatal Intensive Care Unit on infants receiving any breastmilk at discharge (OR 2.0, 95% CI 1.2 to 3.2,  $p = 0.004$ ).

*Staff training (two before/after studies)* Limited evidence suggests that educational interventions delivered to a multidisciplinary staff group may increase health-care professionals' knowledge and can increase initiation rates and duration of breastfeeding. Lack of staff training is an important barrier to implementation of effective interventions.

*Early hospital discharge with home support (two RCTs)* Very limited evidence suggests that this intervention is unlikely to improve and may adversely affect the duration of breastfeeding, although some benefits for infection rates and readmission rates to hospital may occur.

*Organisation of care (four before/after studies)* Baby Friendly accreditation of the associated maternity hospital resulted in improvements in several breastfeeding-related outcomes for infants in neonatal units.

## Economic analysis

Enhanced staff contact, which provided additional skilled professional support in hospital, was found to be more effective and less costly (due to reduced neonatal illness) than normal staff contact in both the base case and the majority of sensitivity analysis

scenarios. Additional support ranged from 0.009 quality-adjusted life-years (QALYs) to 0.251 QALYs more beneficial per infant and ranged from £66 to £586 cheaper per infant across the birthweight subpopulations. Donor milk would become cost-effective if the mechanisms by which it is provided were improved.

## Conclusions

New evidence has been identified to inform care and future research, and the economic analysis is the first in this complex and important field and offers a model for future decision analysis.

Consistent national data are currently lacking on disease and length of stay, individual infant treatment pathways, health and development post discharge and resource use for infants starting life in neonatal units in the UK.

The evidence base mainly relates to infants who are clinically stable. Despite the limitations of the evidence base, kangaroo skin-to-skin contact, peer support, simultaneous breast milk pumping, multidisciplinary staff training and the Baby Friendly accreditation of the associated maternity hospital have been shown to be effective, and skilled support from trained staff in hospital has been shown to be potentially cost-effective. Many of these interventions inter-relate: it is unlikely that specific clinical interventions will be effective if used alone, and particularly in the absence of staff training or of an environment in which mothers are encouraged and supported in having close and ongoing contact with their infants, and to breastfeed/express breastmilk. Several interventions including kangaroo skin-to-skin contact have been shown to be more effective among women who intend to breastfeed.

## Implications for policy and practice

This group of infants should be included in national public health policy developments. National surveillance of feeding, health and cost outcomes for infants and mothers in neonatal units is needed, and consideration should be given to linking this information with Public Service Agreement targets on breastfeeding and infant mortality. There is a need to develop consensus definitions of the initiation and duration of breastfeeding/breastmilk feeding with specific reference to infants admitted to neonatal units

and their mothers; definitions are proposed here. Mothers need to have ongoing encouragement and consistent support for breastfeeding/breastmilk feeding, daily kangaroo skin-to-skin contact with their infants, and facilities to express and store breastmilk. This will require multidisciplinary staff training, continuing support for the Baby Friendly Initiative (BFI) accreditation of maternity units, and improvement of facilities for parents on neonatal units.

## Implications for research

There is a need for high-quality studies that examine feeding and health outcomes of infants and their mothers, developmental outcomes, costs, and the views of staff and parents. Studies should include women from low-income families and from diverse ethnic groups. Preliminary and pilot evaluation work on staff training, 'best practice' kangaroo skin-to-skin contact and peer support is recommended, to be followed by intervention studies as follows:

Level 1 priorities are:

- a study of kangaroo skin-to-skin contact for clinically less stable, possibly very preterm infants and their mothers
- a multifaceted intervention study of a supportive environment and staff training
- a study of peer support in hospital and at home.

Level 2 priorities are:

- studies of single or combined interventions including initiating and sustaining milk production; interim feeding methods; enhancing nutritional composition of breastmilk; and the impact of BFI accreditation of the associated maternity hospital on neonatal care
- a study of staff education, training and behaviour change.



# Chapter I

## Introduction and background

### Infant feeding and health

Breastfeeding is a source of complete nutrition that changes to meet each infant's growing needs, and confers active immunity to disease. The use of breastmilk substitutes is detrimental to the health and development of the infant and child, and to the health of the mother. Despite longstanding methodological challenges in this field, it is now recognised nationally and internationally that the public health implications of infant feeding are important in industrialised countries as well as in resource-poor countries.<sup>1-3</sup> Good-quality, large cohort studies, a large randomised controlled trial and a good-quality systematic review have shown that the absence of breastfeeding increases the risk of short-, medium- and long-term ill health in infants in industrialised countries (e.g. refs 4-8), and adversely affects long-term outcomes in mothers (e.g. ref. 9). Further, data from prospective studies and a large randomised controlled trial show that infants who are not breastfed have worse neurodevelopmental outcomes.<sup>10-13</sup>

Particular care is needed in the interpretation of studies of health outcomes and infant feeding among infants in neonatal units. Studies of infant feeding can seldom be randomised, and there are confounding variables related to the socioeconomic factors associated with infant feeding behaviour. Outcomes measured are often short-term indicators of milk intake or time to discharge, and longer-term health and development outcomes are seldom measured.<sup>14</sup> Studies are often small, as there are relatively limited numbers of infants requiring care in these settings. Because formula feeding and bottle feeding have been standard care for many years, breastfeeding and breastmilk feeding and the techniques required to support them are novel and staff may be unfamiliar with them. Formula is not a standard product across time or across countries or hospitals. Neither can breastmilk be assumed to be standard; even when breastfed, infants can be supplemented with formula or other breastmilk substitutes, and breastmilk is often 'fortified' with commercial preparations depending on the nutritional status of the baby and the policy and practice of the country, unit or individual neonatologist.<sup>15-18</sup> Despite

inconclusive evidence of effectiveness and safety,<sup>19</sup> 'fortification' is such a common procedure in some countries (e.g. the USA) that not all studies report whether or not it is used. Breastmilk can also be enriched by maximising the intake of high-fat components of expressed breastmilk,<sup>20,21</sup> although this is not common practice. Expressed breastmilk can also vary; fresh or stored mother's milk differs from donor milk, which may be derived from one or more mothers at different stages of lactation. Expressed milk may be treated in different ways before being given to the baby. Each of these products is likely to have a different impact on outcomes. Further complicating interpretation is the use of different methods for the oral feeding of both formula and breastmilk. Gavage feeding, bottles and cups may each be associated with different outcomes regardless of the content of the feed.<sup>22-24</sup>

Despite these methodological challenges, it has been shown that for preterm, growth-restricted and sick neonates including those requiring surgery, the use of breastmilk substitutes is associated with increased short- and long-term adverse outcomes including mortality and serious morbidity. Epidemiological studies,<sup>25,26</sup> and randomised and quasi-randomised controlled trials<sup>18,27</sup> in high-risk environments have found that the incidence of invasive infection is higher in low birthweight infants who are fed formula. A meta-analysis of randomised controlled trials<sup>28</sup> has shown that formula-fed low birthweight infants have five times the risk of necrotising enterocolitis (NEC), a condition associated with a mortality of approximately 20% and significant long-term health-care costs amongst survivors.<sup>29</sup> In a UK randomised controlled trial, formula feeding resulted in later transition from parenteral nutrition,<sup>30</sup> increasing the associated cost and infection risk. The studies of neurodevelopmental outcomes cited above indicate a larger deficit in low birthweight infants fed on formula (see, e.g., ref. 31). This finding is particularly important in this group where cognitive impairment is a frequent adverse outcome.<sup>14</sup>

Deaths and serious morbidity as a result of infants in neonatal units consuming contaminated

powdered formula have also been highlighted in the US press ([www.cfsan.fda.gov/~dms/inf-warn.html](http://www.cfsan.fda.gov/~dms/inf-warn.html)). In light of the epidemiological findings and the fact that powdered infant formulas are not commercially sterile products, the US Food and Drug Administration (FDA) now recommends that 'powdered infant formulas not be used in neonatal intensive care settings unless there is no alternative available' ([www.cfsan.fda.gov/~dms/inf-ltr3.html](http://www.cfsan.fda.gov/~dms/inf-ltr3.html); 12 April 2002). The UK Food Standards Agency has informed consumers that powdered infant formula is a non-sterile product ([www.food.gov.uk/news/newsarchive/2007/jul/nonsterile](http://www.food.gov.uk/news/newsarchive/2007/jul/nonsterile); 4 July 2007).

Following discharge from hospital, infants who are not breastfed continue to be exposed to hazards including contamination of feeds and feeding equipment, and errors of reconstitution of formula.<sup>32-35</sup>

Feeding from the breast may facilitate other beneficial outcomes, for example a reduction in procedural pain<sup>36-38</sup> and earlier discharge.<sup>39,40</sup>

Finally, it has been argued that supporting mothers in breastfeeding and providing breastmilk is an essential part of a package of humane care, and assists in promoting attachment.<sup>41</sup> Such care includes gentle touch, decreased negative stimulation, exposure to the mother's scent, skin-to-skin care and family involvement in care,<sup>42</sup> all of which are inherent in breastfeeding. Breastfeeding/breastmilk feeding adds the important factor that the mother's unique involvement in the nutrition and care of her infant may help to ease the inevitable shock, fear and grief following the birth, and decrease estrangement from her baby in the process of care in the high-tech environment of a neonatal unit.<sup>43-46</sup>

## Breastfeeding rates

Breastfeeding rates vary widely internationally. High incidence and prevalence are found in many resource-poor countries,<sup>2</sup> although socioeconomic and geographic differences are apparent and these high rates can be disrupted by factors including conflict and displacement, maternal mortality and ill health.<sup>47</sup> Exclusive breastfeeding, which results in the biggest health gains, is far from universally practised; only 39% of infants are reported as being exclusively breastfed for 4 months following birth.<sup>2</sup> In industrialised countries, the first six or seven decades of the twentieth century saw breastfeeding rates decline steeply. Countries that

have successfully reversed this decline include Sweden, Norway and Japan; Australia and Canada have also seen significant recent increases. Several industrialised countries have, however, not yet achieved such a reversal. These include the USA, France, Ireland and the UK, where low rates of initiation, duration and exclusivity have been observed for several decades.<sup>48</sup> Recent data suggest that initiation rates are increasing in the UK and the USA, although cessation rates have not improved.<sup>49,50</sup>

There is also a marked contrast in breastfeeding rates across different socioeconomic groups in resource-poor countries compared with industrialised countries. The wider availability and promotion of formula is associated with increased formula feeding among the more affluent urbanised populations in resource-poor countries (e.g. ref. 51); recent developments in China, where tens of thousands of infants have become ill as a consequence of substandard formula use, demonstrate the potential adverse consequences of this ([www.bmj.com/cgi/content/full/337/oct01\\_1/a1890](http://www.bmj.com/cgi/content/full/337/oct01_1/a1890)). In industrialised countries, those most likely to formula feed are from the lowest income families (e.g. ref. 49).

## Breastfeeding rates in the UK

Initiation rates in UK countries in 2005 were 78% in England, 70% in Scotland, 67% in Wales and 63% in Northern Ireland,<sup>49</sup> indicating an increase in the previous 10 years. This increase is attenuated but not abolished if data are standardised for the age and socioeconomic composition of the survey sample.

In the same 2005 national survey, the rate of women breastfeeding at all in the UK at 6 weeks after birth was 48% (50% in England, 37% in Wales, 44% in Scotland and 32% in Northern Ireland), demonstrating that the rapid discontinuation of breastfeeding in the first few weeks persists. Exclusive breastfeeding rates are also very low; in 2000 only a quarter of those breastfeeding were breastfeeding exclusively at 2 months. In 2005, 27% of those breastfeeding were breastfeeding exclusively at 2 months, 17% at 3-5 months, 21% at 3 months and 5% at 5 months for the UK overall.<sup>49</sup>

Incidence and prevalence are lowest amongst families from lower socioeconomic groups,<sup>49</sup> particularly among white women compared with those of Asian, black or mixed ethnicity.<sup>49,52</sup> Teenage, young mothers and those least educated

are also vulnerable groups, being half as likely as older mothers to initiate any breastfeeding. The increased prevalence of formula feeding in low-income families is an important contributor to inequalities in health.<sup>53</sup>

### **Breastfeeding rates in neonatal units**

One challenge in measuring breastfeeding rates in neonatal units is that, for these infants, feeding directly from the breast may not be possible. They may instead have breastmilk feeds, which can include fresh or stored mother's own milk, or donor milk, and this milk may be fed by methods including bottle, cup and tube. It is important to distinguish between types of milk and methods of feeding, as they may each have a different impact on health outcomes. This is not always the case in surveys of rates, however, and the information available is limited in this respect. Throughout this report, we use the term 'breastfeeding/breastmilk feeding' whenever it is not possible to differentiate.

The absence of a definition of initiation of breastfeeding and breastmilk feeding specifically for infants admitted to neonatal units in the UK raises further difficulties for measurement of breastfeeding rates among this population. The UK definition for the initiation of breastfeeding is as follows: 'The mother is defined as having initiated breastfeeding if, within the first 48 hours of birth, either she puts the baby to the breast or the baby is given any of the mother's breast milk'.<sup>54</sup>

In the case of infants admitted to neonatal units, it is particularly important to measure both of these components where they occur, namely, the baby receiving human milk (directly through breastfeeding, or with milk expressed by the mother or donor milk) and the mother having initiated breastfeeding or expression of breastmilk. Furthermore, the initiation of breastfeeding may be most usefully measured at the point at which the baby receives a nutritive breastfeed, an event which is likely to involve several occasions of the baby being put to the breast and may occur within days or weeks from birth. The time points for the most appropriate routine measurement of each of these components also require consideration to ensure consistency and to aid comparison with initiation rates among term, healthy infants.

Mothers responding to the 2005 national UK study of infant feeding<sup>49</sup> reported that 5% of their infants were admitted to 'special care'. No difference was

found in initiation of breastfeeding/breastmilk feeding (the survey did not distinguish) according to whether or not the baby started life in a neonatal unit. Infants starting life in a neonatal unit were slightly more likely to be breastfed/have breastmilk both at 1 week (68% of neonatal unit infants compared with 64% of other infants) and at 2 weeks (63% compared with 60%), indicating that mothers were at least as motivated to produce breastmilk for these infants, or that staff encouraged them to do so, or both. This differential increased with the length of time spent in the neonatal unit, with 73% of infants spending at least 4 days in a neonatal unit being breastfed/having breastmilk at 1 week compared with 61% of infants spending only 1 day and 64% not in a neonatal unit at all. Similarly the prevalence of breastfeeding/breastmilk feeding at 2 weeks increased from 58% of infants spending up to 1 day in a neonatal unit to 67% spending 4 or more days.<sup>49</sup>

### **Policy and infant feeding**

The United Nations Global Strategy on Infant and Young Child Feeding<sup>2</sup> recommends that all infants should be exclusively breastfed until 6 months, and that breastfeeding should continue at least until age 2 years. This report states that 'Infants who are not breastfed, for whatever reason, should receive special attention from the health and social welfare system since they constitute a risk group.' These international recommendations on duration and exclusivity of breastfeeding are supported by the governments of England, Wales and Northern Ireland, and there have been a series of policy developments intended to tackle low breastfeeding rates across the four countries in the UK (e.g. ref. 55). Breastfeeding is recognised as contributing to several Public Service Agreement targets and as an important part of the strategy to tackle inequalities in health.<sup>53</sup> Targets have been set to raise both initiation and duration rates.<sup>56</sup> Breastfeeding has been recognised as an important factor in reducing health inequalities in infant mortality,<sup>57</sup> and infants in neonatal care are those most at risk of mortality and serious morbidity. Breastfeeding is also recognised as having a role to play in meeting the Every Child Matters agenda by improving children's health.<sup>58</sup>

Professional bodies and UK NHS organisations have long endorsed breastfeeding as appropriate for all infants (e.g. ref. 1), and recently the National Institute for Health and Clinical Excellence (NICE) recommended a series of interventions across the NHS to raise initiation and duration rates.<sup>3,59</sup>

Statements on breastfeeding/breastmilk for preterm and sick infants are more limited. Strong support is given for breastfeeding/breastmilk for high-risk infants by the American Association of Pediatrics.<sup>60</sup> Recently, the Confidential Enquiry into Maternal and Child Health (CEMACH)<sup>61</sup> specifically recommended that mothers with diabetes should be encouraged to breastfeed for both their own and their infants' metabolic control; these infants are more likely to require care in a neonatal unit. Further, advice that mothers and infants in specific high-risk situations, such as human immunovirus (HIV)-positive mothers, those on antidepressants and substance users, should avoid breastfeeding is now being re-examined in the light of new evidence (e.g. refs 62,63).

There has never been a national UK policy initiative specifically intended to increase breastfeeding uptake and duration for infants in neonatal units, and information about such initiatives in other countries is lacking.

## Factors affecting infant feeding rates in neonatal units

Reasons for the low prevalence of breastfeeding overall include the influence of societal and cultural norms, poor continuity of care in the health services, and a lack of effective care by health professionals in hospital and community.<sup>64-66</sup> These factors are likely to be amplified in the highly medicalised environment of neonatal units, making continuation of breastfeeding/breastmilk feeding difficult for those who do start. Specific factors examined here include the medical condition of infants, the health and well-being of mothers, the neonatal unit environment, the organisation of care, staff training, and the lack of consistent availability of care that would enable breastfeeding in this challenging environment.

## Infants in neonatal units

Infants cared for in special care baby unit (SCBU) neonatal intensive care unit (NICU) settings include:

- Infants born prematurely: these will range from very preterm births, down to 23 weeks, through to those born up to 36 completed weeks. These infants are likely to be low birthweight (LBW; birthweight < 2.5 kg). Some will be of appropriate birthweight for gestational age

(AGA), others will be small for gestational age (SGA).

- Infants born SGA: these are infants whose birthweight falls below a chosen threshold for gestation, most commonly the 10th centile. Some will be preterm infants who are also small for their gestational age, and some term or near term but who are growth restricted. Twins and multiple births will be over-represented in this group, and are more likely to be both preterm and SGA.
- Infants born with or acquiring a health problem that requires additional care: this could include a variety of single or multiple system disorders, congenital malformations (particularly those requiring surgical intervention) and infections. It also includes infants of mothers with problems, for example, they may be infected with HIV or be substance users whose babies may exhibit neonatal abstinence syndrome,<sup>67</sup> and infants admitted with feeding problems and/or weight loss.

As technology has allowed infants to survive at younger gestations, the very preterm, born before 28 weeks, have distinct challenges to their survival, health and development. These infants have had a major impact on the work of neonatal units as they have more complex problems, will require intensive care, and will have an increased length of stay in neonatal units.<sup>68</sup>

There is a strong association between prematurity and multiple births; about 40–50% of twins and 90% of triplets are born prematurely.<sup>69</sup> With improvements in fertility treatment, the already established trend of increasing multiple pregnancies is likely to continue. The issues in relation to breastfeeding twins and multiples are complex and range from simple difficulties relating to the additional time it takes to breastfeed two or more infants, to more complex questions about fulfilling nutritional requirements.

The needs of infants born between 34<sup>+0</sup> and 36<sup>+6</sup> weeks' gestation also require consideration. Although less physiologically and metabolically mature than term infants, they are usually well enough not to need admission to a neonatal unit and are often looked after on the postnatal ward in order to avoid maternal separation. These infants have relatively low oromotor tone and function so are more likely to have feeding difficulties, especially if breastfed, and to require readmission in the first month of life.<sup>70,71</sup>

## Mothers of infants in neonatal units and their families

Mothers of infants in neonatal units are more likely than mothers of term infants to have experienced a complicated labour and/or birth, to be prescribed medication, to have a range of pre-existing social and medical problems, and to be anxious about their children's well-being and even survival.<sup>72</sup> They may have been prescribed antenatal corticosteroids if recognised to be at risk of preterm birth, and this may have a negative impact on milk production.<sup>73</sup> They may have health problems, such as HIV, that require careful consideration of feeding options. They are more likely than mothers of term infants to be from a low-income background<sup>74</sup> and therefore less likely to choose to breastfeed; and, as their pregnancies may be curtailed by preterm labour, they are likely to miss out on the antenatal education that could influence their feeding decision.<sup>75</sup> Women with lifestyle challenges, such as smoking, use of non-prescription drugs and alcohol, will also be over-represented, as these factors predispose to preterm birth and to intrauterine growth retardation.<sup>76</sup> This group of mothers is less likely to have made a decision to breastfeed prior to the often unexpected early birth of their baby.

Mothers will be anxious and concerned about the health and survival of their infant or infants, and they may even be in a different hospital, or discharged home while the infant/infants remain in hospital. They may have to take care of older children, or even return to work if the infant's stay is prolonged. For mothers of twins and multiples, there may be a healthy infant in addition to a sick infant/infants, and it is possible that one infant may be transferred to another hospital for specialist care, resulting in the mother having to choose which baby to spend most time with. Mothers of infants in neonatal units have described being exhausted, feeling insecure bonds with their infants, and experiencing unresolved grief,<sup>45</sup> and the experience of having a small and preterm baby has been described as 'a complete shock', and 'an unnerving experience'.<sup>43</sup> These experiences are likely to have an impact on trying to establish breastfeeding or breastmilk expression.<sup>46</sup>

Family members, especially fathers and grandparents, are likely to be anxious and concerned about the baby, as well as the health and well-being of the mother.<sup>77</sup>

## Neonatal units: organisation of care, staff and ethos

Markedly improved survival rates at all gestations, as well as many more survivors at the extremes of prematurity, mean that there are increasing numbers of infants in neonatal units with complex problems.<sup>14</sup> In addition, the organisation of neonatal care in the UK has undergone substantial reorganisation in the last 5 years with the creation of neonatal networks and the centralisation of neonatal intensive care.<sup>43</sup> These factors combine to give rise to large populations of very small infants with complex needs in big tertiary neonatal units. Almost all units examined in a recent survey reported that they commonly exceeded their capacity, with three-quarters being closed to admissions at some time in the 6 months prior to the survey.<sup>43</sup> This system of care also requires transport of infants, with reported problems related to lack of specialised transport, and communication with parents.

Although the centralisation of care has delivered benefits including streamlining of care, shared meetings, staff training and shared protocols,<sup>43</sup> the promotion of breastfeeding still requires attention. Staff working in neonatal units include neonatal nurses (who are likely to have diverse backgrounds including general nursing, adult intensive care and midwifery), paediatricians, speech therapists, nursery nurses and health-care assistants. Mothers will be cared for by a different set of staff in different settings, including hospital and community midwives, obstetricians, staff in critical and intensive care, health visitors and GPs. A recent learning needs assessment found that NHS staff were not adequately prepared to support breastfeeding among the general population,<sup>78</sup> and that paediatricians were particularly ill-prepared to promote and support breastfeeding.<sup>79</sup> The problems of staff training for breastfeeding have been recognised recently, and NICE has recommended that the Baby Friendly Initiative becomes the minimum standard for care for NHS trusts.<sup>3,59,80</sup> However, although neonatal units are assessed to a limited degree as part of the Baby Friendly assessment of the maternity unit, there is as yet no Baby Friendly accreditation process for standards of care in neonatal units. Neonatal nurses and medical staff are therefore likely to be poorly trained in the complexities of supporting breastfeeding in this environment, including the skills needed to work with mothers of multiples;<sup>81</sup> midwives and health visitors are unlikely to

have the skills to support women to express breastmilk over long periods of time; and each discipline is likely to differ in their preparation for and approach to infant feeding, resulting in inconsistencies in approach.

These problems are compounded by understaffing. The national shortage of neonatal nurses means that the British Association of Perinatal Medicine guidelines<sup>82</sup> of one nurse to one NICU patient are seldom adhered to; only 4% of neonatal units meet these standards, and the nurse workforce is understaffed by one-third.<sup>43</sup>

Neonatal units are stressful for staff and students, as well as families. All the infants are ill or very small, parents are visibly anxious, staff are busy and concerned about the infants' well-being and even survival. The atmosphere has been described as 'stressful', 'frightening' and 'difficult'.<sup>83</sup> Parents need support from staff; some parents have described themselves as 'completely overwhelmed', and that 'it felt like [their baby] belonged to the NHS and not to us'.<sup>43</sup> Equipment is essential and pervasive, including incubators, monitors and pumps.

Facilities may not be ideal for providing appropriate care. Finding space for parents to sit quietly with each other, to talk with staff, or to sit beside the baby and take in the fact of an unexpected preterm birth, a congenital problem, or an episode of worsened health status, can be problematic. In a recent survey, 25% of mothers reported that units had no facilities for them to stay in or close by the unit.<sup>43</sup> The lack of space beside incubators can make prolonged skin-to-skin care difficult or even impossible. The same report found that 25% of mothers 'never' had skin-to-skin care with their infants, and 60% sometimes felt they were 'in the way'.<sup>43</sup>

In such settings, the promotion of humane care becomes problematic.<sup>41–44</sup> It is widely accepted in the care of healthy, term infants that close contact between baby and mother is essential for breastfeeding, for attachment and for the well-being of the baby and the mother,<sup>84</sup> and the lack of this contact adds to the vulnerability of mothers and infants in neonatal units. A system of care that includes reducing noise and light, minimal handling, and giving longer rest periods, known as developmental care (NIDCAP), has been instituted in some units internationally. Although the evidence base examining this form of care is limited, outcomes identified include decreased

moderate–severe chronic lung disease and NEC, and improved family outcomes.<sup>85</sup>

## **Breastfeeding/breastmilk feeding in neonatal units**

Several factors influence breastfeeding/feeding with breastmilk in neonatal units.

Breastmilk production, and in particular the copious production of milk known as lactogenesis II, is delayed in women having a preterm birth, and this may be further complicated in women who have had antenatal corticosteroids.<sup>73</sup> Mammary growth may be incomplete, and the placental lactogen required for mammary development could also be impaired.<sup>86</sup> Establishing and sustaining lactation is much more complex than for mothers of healthy infants,<sup>87</sup> expressing milk without the satisfaction of having a baby to feed can be demanding and disheartening,<sup>21</sup> and expression often needs to be sustained over a prolonged period of time – the mean length of stay for infants in neonatal units in the UK is 55 days.<sup>43</sup>

Mothers who have had a complicated birth including caesarean section, or who are themselves ill, will have major problems in expressing milk and visiting their infant, and will be unable to spend the close and intimate time needed to help establish breastfeeding/breastmilk supply.<sup>88</sup>

It becomes increasingly hard for the mother to sustain milk production in the absence of direct feeding from the breast, often resulting in poor weight gain and growth. In order to promote growth clinicians either increase the volume of milk an infant is fed or supplement breastmilk. This is done by 'fortification' using a multinutrient breastmilk fortifier or individual supplements (protein, carbohydrate, fat and minerals) or supplementing intake with a preterm infant formula. Evidence on short- and long-term benefits and adverse effects of these practices is inconclusive.<sup>19</sup> Practice on this issue differs internationally and across different units in the UK, and there are concerns about the increased osmolality that results when breastmilk has commercial products added.<sup>89</sup> The psychological impact of implying to a mother that her milk is nutritionally inadequate is unknown but could be profound. Some units offer increased concentrations of hindmilk as a method of fortification,<sup>90</sup> although evidence is lacking on the consequences for the infant in terms of growth, development and health.

Treatment and storage of mother's own expressed breastmilk, whether fresh, frozen or pasteurised, is critical both for the baby's intake and for the mother's motivation to continue to express. Staff need to be trained and to have the facilities to ensure proper storage and use.<sup>3</sup>

When mother's own milk is not available or not sufficient, donor milk can provide a high-quality substitute. A recent unpublished study at Guy's and St Thomas' Hospital in London found that the establishment of a donor human milk bank was associated with a substantial increase in the provision of maternal breastmilk to infants with a birthweight of less than 1500 g at the time of discharge. Fifty per cent of infants received breastmilk at discharge before the milk bank opened, whereas 78% received breastmilk on discharge 18 months after their milk bank opened (Dr Camilla Kingdon, St Thomas' Hospital and Association for Milk Banking, personal communication, 2008). An efficient milk bank system is not widely available in the UK;<sup>91</sup> NICE is currently examining this issue ([www.nice.org.uk/guidance/index.jsp?action=byID&o=11973](http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11973)).

The transition to oral feeds is challenging as a result of the uncoordinated suck and swallow pattern of preterm and low birthweight infants.<sup>92-94</sup> Infants may not be able to tolerate oral feeds, will have problems of temperature control, may be difficult for parents to handle, and may have respiratory, cardiac, neurological or other problems that make oral feeding complicated. They may have nasogastric tubes and intravenous (i.v.) lines in place. Difficulties exist for all oral feeding methods,<sup>95</sup> but breastfeeding is especially challenging if conducted in an environment where staff do not have the special skills needed, women are anxious about handling a fragile baby, facilities are not available for privacy, and milk supply may not be well established.<sup>81,96</sup> There is concern that giving the baby bottle teats or pacifiers may complicate the transition to feeding directly from

the breast as the feeding action is different from breastfeeding,<sup>97,98</sup> and alternatives including cups and nasogastric and orogastric tubes have been used to avoid this.<sup>99</sup> However, staff may find it more time consuming to help a mother to breastfeed or support her to express and store her milk than using formula or feeding from a bottle as these have been standard practice for some time.

Hospital protocols may interfere with breastfeeding/breastmilk feeding; these may relate to infants' expected weight gain and growth, feeding frequency or mode of feeding. Such protocols are likely to be based on current standard care, which in the UK is more likely to be formula feeding.

A consistent strategy to promote breastfeeding/breastmilk feeding in neonatal units is lacking.<sup>100</sup> Without such a strategy at national and unit levels, the combination of the stressful environment and the lack of skills needed to support breastfeeding/breastmilk feeding in these vulnerable infants and their mothers is likely to result in inconsistent and ineffective care.

## Conclusion

It is in this complex context that this review and economic analysis are set. The work is both timely and important, as this topic has the potential to have an impact on the mortality and morbidity of preterm and low birthweight infants, and the health and well-being of mothers, and to have considerable resource implications for the health service. Recognising the range of factors that affect the mother, infant, caregivers and the health service, and the potential of this topic to have an impact on inequalities in health, we sought to examine not only the clinical interventions that might work but also the public health context. This study includes work to examine both the effectiveness and cost-effectiveness of interventions.





## Chapter 2

# Aims and objectives of the study

### Aims

This study, which includes a systematic review and a decision model, was commissioned by the NIHR Health Technology Assessment programme. The specific aim was to evaluate the effectiveness and cost-effectiveness of interventions that promote breastfeeding or feeding with breastmilk for infants admitted to neonatal units.

This study aimed to evaluate the impact of all types of breastfeeding promotion intervention among infants admitted to neonatal units. These could range from national policies that aim to support the mother in her role as prime carer, such as paid maternity leave, through to clinical interventions such as interim feeding methods, and education and support programmes that aim to increase women's understanding of, and ability to, breastfeed their infants. The decision model focused on evaluating the impact of support, specifically enhanced staff support, on the long-term health of the infant.

### Objectives

The specific objectives of this study were to:

- identify and describe health promotion activity intended to increase breastfeeding or

feeding with breastmilk for infants admitted to neonatal units

- evaluate the effectiveness of any such health promotion activity, in terms of changing the number of women who breastfeed or feed with breastmilk, using the Ottawa Charter for Health Promotion framework<sup>101</sup>
- analyse the cost-effectiveness of health promotion activity, specifically enhanced staff support, using a critical review of the existing cost-effectiveness literature and the development of a decision model
- collate expert opinion on best practice, using the views of Advisory Group members and information from neonatal unit settings nationally and internationally where breastfeeding/breastmilk feeding rates are high
- identify implications for policy, practice and education based on the findings of this study
- identify an agenda for future research that will inform key gaps in knowledge.

This study was informed by an Advisory Group including academic, clinical and service user/ consumer colleagues and a subgroup of clinical advisers (Appendix 1).



## Chapter 3

# Scope and methods of the effectiveness and health economics reviews

### Effectiveness review

A systematic review of the literature was undertaken using guidelines published by the Centre for Reviews and Dissemination.<sup>102</sup>

### Inclusion and exclusion criteria for studies in the effectiveness review

#### Participants

This review included only studies that recruited infants or the mothers of infants who were admitted to neonatal units. The eligible infant population included preterm infants (both healthy and sick) and full-term infants who were growth restricted and/or sick. Twins and multiple births were eligible for inclusion, as were infants with congenital abnormalities, feeding problems, hypoglycaemia or jaundice, and those requiring surgery.

Studies recruiting population subgroups of mothers of eligible infants, such as mothers from low-income groups or different ethnic groups, were also eligible. Studies of interventions targeting other people were also considered: these participants included those linked to women who may breastfeed, such as partners, other family members or health professionals.

#### Interventions

This review included evaluations of any type of intervention that addressed breastfeeding/feeding with breastmilk in neonatal units, and studies that comprised a domiciliary care component following discharge from the unit. Control groups could receive standard or routine care or an alternative breastfeeding promotion intervention.

As the aim of this review was to examine breastfeeding-/breastmilk-related interventions in neonatal units, evaluations of interventions that were implemented during the antenatal period were excluded.

Studies that examined the effectiveness of breastmilk on clinical outcomes (e.g. studies

that examined associations between breastmilk consumption and the incidence of necrotising enterocolitis, NEC), studies that evaluated the nutritional content of formula and breastmilk fortifiers, and studies of the establishment and maintenance of milk banking were outside the scope of this review of effectiveness.

#### Outcomes

A study must have reported a breastfeeding-/breastmilk-related outcome to be included in this review of effectiveness. These may have included breastmilk composition and volume, tasting dripped breastmilk, number of sucks, initiation of breastfeeding, any breastfeeding, exclusive breastfeeding and rates of breastfeeding at discharge and beyond. Studies that did not report a breastfeeding-/breastmilk-related outcome were excluded.

Secondary outcomes of interest included clinical/health outcomes (e.g. NEC, gastrointestinal disease, weight), process outcomes (e.g. time of hospital discharge, readmission, time spent by mother in contact with baby), psychosocial outcomes (e.g. views of mothers, fathers, families, health-care staff) and cost-effectiveness outcomes.

Outcomes were examined to assess the different gestational ages of the infant and/or ability to coordinate sucking and swallowing: for example, practice and outcomes for skin-to-skin care may be different for extremely low birthweight infants compared with low birthweight infants, and for infants with specific neurological problems.

#### Study designs

Randomised controlled trials (RCTs) and non-RCTs with concurrent controls were included in this review. For categories of interventions where evidence was limited and in recognition of the difficulties inherent in evaluating certain types of health promotion intervention, exceptions to this rule were considered. For example, multifaceted changes to organisation of care may have been conducted using a comparative study with retrospective controls or a before- and after-

intervention design. Before/after studies that had utilised a cohort or cross-sectional study design were eligible for this review. It is important to note that results from these studies are likely to be less robust than those from RCTs and non-RCTs, and any reported effect on breastfeeding outcomes may not be solely attributable to the intervention(s). Studies without any form of control group (i.e. descriptive studies) and case studies were excluded.

We identified systematic reviews to assist with identification of eligible primary studies. Findings from identified systematic reviews were not included as a source of evidence for this review. This was due to differences in quality and methodological approaches across reviews for the analysis of primary studies, which may have been included in more than one review.

### Identification of studies

The search strategies were devised in collaboration between the information officer (KM) and members of the research team familiar with the topic area. There was no limit by language or country of origin. Studies in this review were identified by searching a wide range of medical, nursing, psychological, sociological and grey literature databases. Each search strategy was developed for MEDLINE and adapted for use with other databases (see Appendix 2.1). In order to minimise potential publication bias for the effectiveness review, the search process aimed to identify published research, unpublished research or research reported in the grey literature, through the following four stages:

#### Search to identify systematic reviews

Searches were carried out to identify systematic review literature published in this field. Databases were searched for studies dated from 2006 to January 2008. Searches were limited to retrieve only systematic reviews. A total of 115 references were retrieved.

The following databases were searched:

- MEDLINE and MEDLINE In-Process Citations
- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effectiveness
- Health Technology Assessment Database
- National Research Register
- Scottish Intercollegiate Guidelines Network
- National Guidelines Clearinghouse
- Health Services/Technology Assessment Text
- Turning Research into Practice

- Health Evidence Bulletins Wales
- Clinical Evidence.

#### Search to identify primary studies

All databases were systematically searched for primary studies dating from inception to August 2007. A pragmatic search of selected databases was undertaken in January 2008. The databases marked below (\*) were identified for update searching based on yield of included studies. A total of 14,729 references were retrieved by both original and update searches.

The following databases were searched:

- \*MEDLINE and MEDLINE In-Process Citations
- \*EMBASE
- \*CINAHL
- \*Maternity and Infant Care
- \*PsycINFO
- \*British Nursing Index and Archive
- \*Health Management Information Consortium
- \*Cochrane Central Register of Controlled Trials
- \*Science Citation Index
- \*Pascal
- \*Inside Conferences
- \*Dissertation Abstracts
- Sociological Abstracts
- Latin American and Caribbean Health Sciences
- Applied Social Sciences Index and Abstracts
- Index to Theses
- MetaRegister of Controlled Trials
- National Research Register.

#### Search for studies evaluating galactagogues

As part of an iterative approach to searching, an additional search was undertaken to identify studies of galactagogues. Databases were searched for studies dated between 1991 and February 2008. Searches were not limited by study design. A total of 4045 references was retrieved.

The following databases were searched:

- MEDLINE and MEDLINE In-Process Citations
- EMBASE
- CINAHL
- Maternity and Infant Care
- PsycINFO
- British Nursing Index and Archive
- Health Management Information Consortium
- Cochrane Central Register of Controlled Trials
- Science Citation Index.

To identify grey literature and unpublished studies and to check for completeness, bibliographies of studies retrieved were hand searched, and experts on the Advisory Group were asked to assist with the identification of other published or unpublished studies.

## Data handling process

Titles and abstracts of bibliographic records were imported into ENDNOTE 9 bibliographic management software and duplicate records removed. Two reviewers independently screened titles and abstracts of identified records. Any disagreements were resolved by consensus. This process identified 138 potentially relevant studies. Full papers were ordered and assessed for inclusion using a prescreen form (see Appendix 3) by one reviewer and checked by a second. Any disagreement on whether a paper was relevant to the review was resolved by a third reviewer.

The five areas of health promotion action identified in the Ottawa Charter for Health Promotion<sup>101</sup> were used as a framework to assist in classification of the different types of intervention to promote breastfeeding among infants in neonatal units. These were:

- public policy such as legislation, fiscal measures (e.g. maternity leave)
- supportive environments that protect natural resources and generate healthy living and working conditions (e.g. private rooms for expressing, provision of pumping equipment to express at home)
- community action that uses existing human and material resources to enhance self-help and social support (e.g. social support through family, peers)
- development of personal skills through the provision of information, education for health, and enhancing life skills (e.g. education programmes, clinical support)
- reorientation of health services to promote health (e.g. staff training, the BFI).

Standardised data extraction and quality appraisal tables were adapted from the Centre for Reviews and Dissemination (CRD) Report 4.<sup>102</sup> Data were extracted and appraised for quality by one reviewer and checked by a second reviewer (see *Tables 26–73* in Appendix 4.1). An overall quality rating was awarded to each study based on NICE guidance development methodology<sup>103</sup> and the Cochrane Handbook (2008)<sup>104</sup> (see *Tables 74–87* in Appendix

5). Any disagreements in data extraction or quality appraisal were resolved by discussion or, if necessary, by a third reviewer. Details of studies that were excluded at either the prescreening or data extraction stage are shown in Appendix 6.1.

Five relevant systematic reviews were identified in the course of the searches. These were used to identify studies. Data extraction forms for these reviews are given in Appendix 7.

## Analysis and presentation of results

Quality ratings for each study have been presented in the text (Chapter 4) using the following definitions:

- Good quality – most or all criteria being fulfilled and where they were not met, the study conclusions were thought very unlikely to alter.
- Moderate quality – some criteria being fulfilled and where they were not met, the study conclusions were thought unlikely to alter.
- Poor quality – few criteria were fulfilled and the conclusions of the study were thought very likely to alter. Serious caution is warranted in interpretation of the results of these trials.

Details of the individual quality ratings for each study are provided in Appendix 5.

Within each topic area, results are presented first for RCTs and then for other study designs.

Results from all primary studies were assessed and summarised in a qualitative synthesis for each type of intervention (Chapter 4) and across types of intervention (Chapter 7). Meta-analysis was not considered appropriate due to the heterogeneity between studies for type of intervention, standard care, characteristics of participants, outcome measures, feeding intention and country settings. Relative risks for outcomes have been estimated for individual studies on an intention-to-treat (ITT) basis where appropriate outcome data were reported. Given the relatively high clinical risk among the target population, the ITT analysis was adjusted for legitimate postrandomisation exclusions. These were calculated as infants who were lost to the study due to death, not achieving predefined clinical stability to participate in the intervention, or other clearly defined inclusion or exclusion criteria such as discharge to original hospital. Data from studies rated as good or

moderate quality have been presented in forest plots where appropriate. In the absence of meta-analyses, funnel plots and sensitivity analyses were not considered appropriate methods to assess publication bias.

Throughout the report, included studies are referred to using the name of the first author and the date, e.g. Jones 2001, or the citation number.

Results of the effectiveness review are presented in full in Chapter 4, and for the economic modelling in Chapter 5. Due to the inter-related nature of results from each topic area, results are summarized and discussed together in Chapter 7.

## Methods of health economics literature review

### Inclusion criteria

Studies were eligible if they were full economic evaluations (i.e. they included an explicit comparison of both costs and effects for an intervention and at least one comparator), and were considered to be useful in answering the research question relating to cost-effectiveness.

### Identification of potential economic evaluations

The search strategies were devised in collaboration with an information specialist. There was no limitation by language or country of origin. A search strategy was developed for NHS Economic Evaluation Database (NHS EED) and adapted for use with other databases. Full details are presented in Appendix 2.1.

The search process was undertaken in three stages:

*1. Searches of health economics resources* The following resources were searched to identify economic evaluations:

- NHS Economic Evaluation Database (NHS EED) (up to 2007/08/8) (internal CRD interface)
- Health Economic Evaluations Database (HEED) (up to 2007/08/08) (internet)
- Pediatric Economic Database Evaluation (PEDE) (1980–2003) (internet) <http://pede.bioinfo.sickkids.on.ca/pede.search.jsp>.

A total of 294 references were retrieved.

*2. Subset search of Clinical Effectiveness Endnote Library* An Endnote Library containing 10,262 references, identified by the search undertaken for the evidence of effectiveness review search detailed above, was searched to identify potentially relevant cost/economic studies. After deduplication, 1176 records were identified.

The following terms were entered line-by-line ( \_ indicates a space):

- \_cost\_
- \_costs
- \_cost-
- \_costly
- \_costing
- \_econom
- \_budget
- \_price
- \_pricing
- \_expenditure
- value for money

A total of 1176 references were retrieved and scanned for relevance.

*3. Further searches to populate the decision model* A series of focused supplementary searches were undertaken to identify data to populate the model. These searches were limited to a small collection of ‘core’ databases, as specified by the health economists:

- NHS Economic Evaluation Database (NHS EED) (up to 2008/02/28 (internal CRD interface)
- Health Economic Evaluations Database (HEED) (up to 2008/02/28) (internet)
- MEDLINE and MEDLINE In-Process Citations (2003–2008/02/wk 2) (OVID)
- EMBASE (2003–2008/wk 7) (OVID)
- EconLit (2003–2008/01) (OVID).

Searches were undertaken for three supplementary topics:

1. long-term outcomes of NEC or sepsis
2. quality of life in infants with NEC, sepsis, meningitis, etc.
3. economic evaluations of NEC, sepsis, meningitis, etc. in preterms or neonatal units.

Totals of 713 (topic 1), 99 (topic 2) and 487 (topic 3) references were retrieved for the searches and scanned for relevance.

## Results of health economics review

No economic evaluations that met the inclusion criteria were identified. Had suitable studies been identified, data would have been extracted (Appendix 4.2). Details of excluded studies are presented in Appendix 6.1, along with information on the planned quality appraisal process.

## Framing recommendations

To inform implications for policy, practice and education, and to identify gaps in the evidence base and priorities for future research, two additional approaches were used:

- Seven expert clinical advisors from neonatal units in Sweden, the USA and the UK

(Appendix 1) were asked to identify key factors in their experiences of introducing successful breastfeeding-/breastmilk feeding-related change into their units (Chapter 6). This information was used to reflect on the findings of the study (Chapter 7).

- After reading the findings of the study, Advisory Group members were asked to agree implications for policy, practice and education (Chapter 8) and to agree prioritisation of suggestions for future research studies (Chapter 9). Studies with methodological weaknesses, which were considered likely to have potentially misleading results, were not used in framing the implications for policy, practice and education.





## Chapter 4

### Results of the effectiveness review

#### Summary of review flow

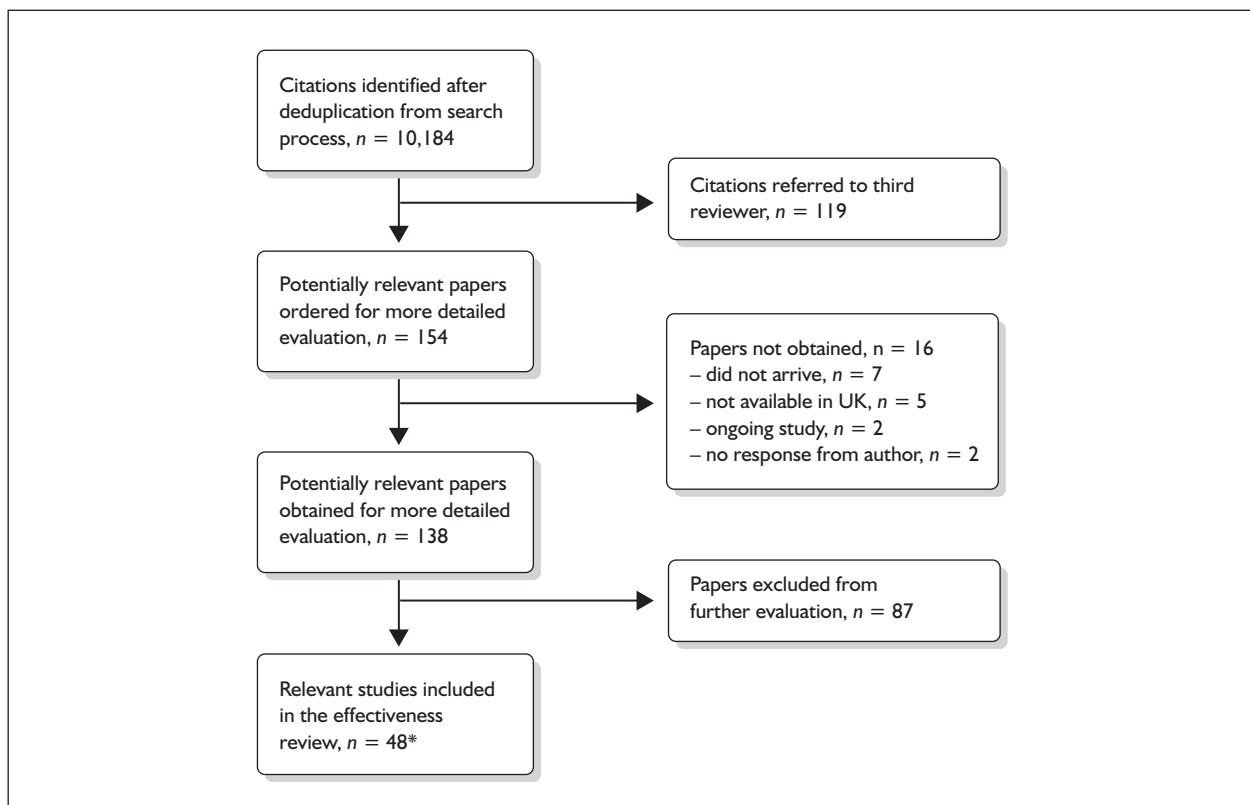
The flowchart (*Figure 1*) is based on the QUOROM statement flow diagram<sup>105</sup> to summarise the results of the methodology described in Chapter 3.

As detailed above, only 1% (119/10,184) of the total citations identified following deduplication were referred to a third reviewer for resolution regarding their potential relevance to this effectiveness review. Decisions regarding these citations were largely uncontroversial and, where any uncertainty remained, full papers were sought for further evaluation. Decisions regarding exclusions during the prescreening process were largely uncontroversial with the exception of one study (Sisk *et al.* 2006),<sup>106</sup> which was excluded on the grounds that this study was not an evaluation of an intervention.

#### Summary of evidence base

A total of 48 studies evaluating the effectiveness of interventions to promote breastfeeding in neonatal units met the inclusion criteria for this review. Of these studies, 65% (31/48) were randomised controlled trials (RCTs). The results of two studies were reported in two separate papers<sup>107–110</sup> and Hill was reported in three separate papers.<sup>111–113</sup> One paper reported findings for two types of intervention presented in this review, with each intervention having been evaluated by a different study design method.<sup>114</sup> For the purposes of this review, this paper has been counted as two studies.

The five identified systematic reviews assisted with the identification of a total of 29 included primary studies including 22 RCTs,<sup>107–110,114–133</sup> one randomised crossover study<sup>134</sup> and six other forms of controlled studies.<sup>135–139</sup>



**FIGURE 1** QUOROM statement flow diagram summarising the methodology. \*Reported in 51 papers.

A further 19 primary studies were identified through our independent search methods for inclusion in this review. These included nine RCTs,<sup>113,140–147</sup> two randomised crossover studies<sup>114,148</sup> and eight other forms of controlled studies.<sup>20,81,149–154</sup>

## Definitions of topic areas

The 48 included studies were grouped into nine topic areas, considered in detail in the following sections. Definitions of these topic areas and related issues are as follows:

### **Increased mother and infant contact interventions**

Relevant interventions are those that promote warmth, developmental care, and early and successful breastfeeding for infants in need of special care. This includes skin-to-skin contact, which is defined as any contact between the mother's and the infant's skin over any period of time, usually from birth,<sup>155</sup> and kangaroo mother care (KMC). KMC was originally developed in Colombia and comprises three components: (1) ongoing skin-to-skin contact in the kangaroo position, namely, between the mother's breasts in an upright position; (2) kangaroo feeding policy, which is frequent and exclusive breastfeeding; (3) kangaroo discharge policy, which is early discharge from hospital regardless of weight or gestational age.<sup>107</sup> The use of KMC to optimise extrauterine transition in term<sup>154</sup> and preterm<sup>157,158</sup> infants is generally accepted as a safe intervention with multiple physiological advantages.<sup>159</sup> The potential of KMC to increase breastfeeding rates, resulting in associated physiological and emotional benefits, is, however, less established.

### **Interim feeding methods and related interventions**

'Interim feeding methods' refers to the range of enteral feeding methods used to give babies either breastmilk or other fluids until feeding from the breast is possible. Enteral feeding is the administration of any feed into the gastrointestinal tract.<sup>155</sup> Feeding from vessels other than the breast may be necessary if the infant is too small or sick to take the breast directly or because the mother is unavailable; thus such methods may be used to replace or supplement feeding from the breast.

Interim feeding methods used include feeds given by nasogastric or orogastric tube or from vessels including bottles, cups, spoons and syringes. Some methods specifically aim to avoid the use of

artificial teats on the rationale that learning to feed using a teat may make the transition to the breast more difficult. Such methods include cups, spoons and syringes, as well as 'finger feeding', where a nasogastric tube is attached to the finger of the carer and inserted in the infant's mouth. Nipple shields are sometimes used with the aim of making feeding directly from the breast easier for small and sick babies.

'Related interventions' describes interventions used with the aim of enhancing feeding behaviours. This includes the use of pacifiers, which can be used for the purpose of enhancing non-nutritive sucking or in an effort to calm the infant. One alternative offered is the use of carers' fingers.

### **Expressing breastmilk interventions**

Relevant interventions include those that mothers may use to remove breastmilk from their breasts. The purpose of expression is normally twofold: to stimulate milk production, and to provide breastmilk for infants until they are able to satisfy their nutritional needs by feeding directly from the breast or until they are no longer receiving breastmilk. Variables of interest in the expression of breastmilk include both the equipment or technique that mothers may use for milk removal and the regimens for their use. Breastmilk may be expressed by hand and/or by pump; pumps may be hand- or foot-operated, or battery or electrically powered. Regimens may specify how, how often, how long or how much to express.

### **Additional interventions to enhance breastmilk production**

Relevant interventions are those that mothers may use, usually in association with expressing breastmilk and/or breastfeeding, with the intention of increasing the volume of breastmilk produced. Such interventions include pharmacological (galactagogue medication) or dietary interventions, or interventions aimed at facilitating the mother's let-down reflex with relaxation techniques or use of items such as photographs that she associates with her infant.

### **Interventions to support optimal nutritional intake from breastmilk**

Relevant interventions include those that aim to optimise the quality and/or quantity of the breastmilk fed to infants in neonatal units and following discharge. Interventions may include test weighing infants before and after feeds, measuring the fat content of expressed breastmilk, and

feeding hindmilk to increase the energy content of milk.

### **Breastfeeding education and support interventions**

Relevant interventions include those that aim to offer support, education and/or counselling to parents of babies in neonatal care settings, and to take place either in hospital or at home during an infant's hospital stay, or following discharge. Interventions may be offered by professionals or peers on a one-to-one or group basis and using a range of strategies including oral communication via face to face or telephone methods or written information via leaflets and other materials.

### **Staff training interventions**

Interventions that aim to improve health-care professionals' knowledge, skills and behaviour in relation to lactation and breastfeeding, and practices to support and promote breastfeeding and breastmilk production by mothers of infants in neonatal units.

### **Early hospital discharge with home support interventions**

Early hospital discharge with home support intervention refers to discharge of infants prior to those infants having met standard weight gain criteria and/or having moved from gavage to full oral feeds. In most, but not necessarily all, cases, this intervention is conducted among clinically stable infants, defined as ones without cardiorespiratory compromise and maintaining normal body temperature when fully clothed in an open cot. Education and support of parents may be provided in the community setting following such discharge. Early discharge as part of comprehensive KMC is discussed below under 'Increased mother and infant contact intervention'.

### **Organisation of care interventions**

Relevant interventions are those that change care at the level of the individual unit (intra-unit) or between units (inter-unit). Both groups of intervention aim to improve the organisation of a single or allied health service or care within that service, to promote and support breastfeeding. These interventions are mostly, but not necessarily, conducted in hospital settings and may have several components implemented at one time. The changes to organisation of care may be implemented at the level of the hospital or the neonatal care unit or between hospitals or neonatal care units, as in the case of a managed clinical network.

## **Standard care**

Standard or routine care was highly variable between studies and settings and often described in insufficient detail. Details of standard care or comparison group(s), where available, are provided for each study within each of the results sections below.

## **Initiation and duration of breastfeeding or feeding with breastmilk**

The specific time points at which outcomes (such as initiation or duration of breastfeeding) were assessed varied between studies and in some cases were inadequately described. Definitions used by study authors are reported in the results sections below. These may or may not be consistent with the definitions adopted for the purposes of this review in accordance with the Department of Health definition for initiation of breastfeeding for the general population (see Glossary).

Included studies, the topic addressed, and whether or not they have been included in previous systematic reviews, are summarised in *Table 1*.

## **Increased mother and infant contact interventions**

A total of 12 primary studies evaluating mother and infant contact interventions were identified. As detailed in *Table 2*, nine primary studies were included in at least one of the three identified systematic reviews. Seven<sup>115,121,129,135,139,147,150</sup> of the 12 studies were conducted in industrialised country settings including one in the UK.<sup>147</sup>

## **Results from randomised controlled trials**

Nine randomised controlled trials of mother and infant contact interventions were identified<sup>107,108,115,118,121,129,131,132,141,147</sup> (*Tables 26–34* in Appendix 4.1).

### **Characteristics of participants**

Four of the trials were conducted in industrialised country settings including one in the UK,<sup>147</sup> two in the USA<sup>115,121</sup> and one in Australia.<sup>129</sup> Of the remaining five trials, one was a multicentre trial conducted in Ethiopia, Indonesia and Mexico<sup>131</sup> and one was a pilot RCT conducted in India.<sup>118</sup> The other three trials were conducted in Colombia,<sup>107,108</sup> Ecuador<sup>132</sup> and Malaysia.<sup>141</sup>

**TABLE 1** Included studies by topic and study design, and whether identified in a previous systematic review (SR)

Topic	Subgroups of intervention	No. of systematic reviews (SRs)	No. of studies in SRs (no of RCTs)	No. of extra primary studies (no of RCTs)	Total no. of primary studies (RCTs)
Increased mother and infant contact	Kangaroo care, skin-to-skin	3	9 <sup>a</sup> (7)	3 (2)	12 (9)
Interim feeding methods and related interventions	Nasogastric tube, bottle, cup, nipple shields, pacifiers	3	6 (5)	0	6 (5)
Expressing breastmilk	Electric and pedal pumps, manual, frequency of expressing	1	4 <sup>b</sup> (3)	2 (2)	6 (5)
Enhancing breastmilk production	Galactagogues, relaxation, therapeutic touch	2	3 (3)	4 <sup>b</sup> (2)	7 (5)
Supporting optimal nutritional intake from breastmilk	Mothers' measures of creatinocrits, breastmilk intake weights, hindmilk feeds	0	0	3 (2)	3 (2)
Breastfeeding education and support	Peer or professional support, community or hospital based. Education for mothers	2	3 (2)	3 (1)	6 (3)
Staff training	Training or education of health professionals	0	0	2 (0)	2 (0)
Early hospital discharge with home support	Home visits and support including home gavage feeding	3	2 <sup>c</sup> (2)	0	2 (2)
Organisation of care	Policy, protocol-based care, BFI or non-BFI standard(s)	1	2 (0)	2 (0)	4 (0)
<b>TOTAL</b>		<b>5<sup>d</sup></b>	<b>29 (22)</b>	<b>19 (9)</b>	<b>48 (31)</b>

a Charpak 1997<sup>107</sup> and Charpak 2001<sup>108</sup> relate to the same study.  
b Jones 2001<sup>114</sup> reports findings from an expressing breastmilk intervention (RCT) and an enhancing milk supply intervention (randomised crossover study) in the same paper and appears in each of those sections.  
c One systematic review (SR) (Edmond 2006<sup>155</sup>) included another SR,<sup>160</sup> which was reporting on one RCT<sup>109,110</sup> (Ortenstrand 2001, 1999). The SR has only been counted in the numbers of SRs and not as one of the included studies within an SR.  
d Three SRs (Edmond 2006;<sup>155</sup> McInnes 2006;<sup>161</sup> Collins 2006<sup>162</sup>) have reviewed several intervention areas and appear across intervention categories. Two SRs (Flint 2007;<sup>163</sup> Conde-Agudelo 2003<sup>164</sup>) reviewed one topic.

All trials recruited infants according to criteria of birthweight or gestational age. Four trials<sup>115,121,141,147</sup> focused on infants with the internationally recognised definition of very low birthweight (< 1500 g). The remaining trials used a variety of birthweight criteria, including infants with a birthweight of 2000 g or less,<sup>107,108,132</sup> 1000–1999 g<sup>131</sup> and < 1800 g.<sup>118</sup> The Colombian trial (Charpak 1997, 2001)<sup>107,108</sup> included some infants [intervention (I):132/382; control (C): 155/364] who had a birthweight of 2000 g or less and were eligible to participate in the intervention but were not admitted to the neonatal unit. The remaining trial focused on infants at ≥30 weeks' gestation.<sup>129</sup>

All trials focused on infants who were clinically stable. Two trials included infants on minimal ventilatory support.<sup>121,141</sup> The remaining trials included infants who did not require oxygen equipment<sup>147</sup> and were gavage fed,<sup>115</sup> on oral feeds,<sup>118</sup> tolerant of enteral feeds<sup>129,131,132</sup> or demonstrating a satisfactory suck and swallow reflex.<sup>107,108</sup>

Characteristics of maternal participants are limited and variable across trials. One of the nine trials focused on mothers from a range of social and economic settings.<sup>131</sup> Of the remaining trials that reported socioeconomic data, two trials

**TABLE 2** Included studies for 'Increased mother and infant contact interventions'

Primary paper	Study design No. analysed <sup>a</sup>	Inclusion in existing systematic review	Country
Cattaneo 1998 <sup>131</sup>	RCT <i>n</i> = 100 (site 1) <i>n</i> = 104 (site 2) <i>n</i> = 79 (site 3)	Conde-Agudelo 2003 <sup>164</sup> Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	Ethiopia, Indonesia and Mexico
Charpak <sup>b</sup> 1997 <sup>107</sup>	RCT <i>n</i> = 746	Conde-Agudelo 2003 <sup>164</sup> Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	Colombia
Charpak <sup>b</sup> 2001 <sup>108</sup>		Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	Colombia
Sloan 1994 <sup>132</sup>	RCT <i>n</i> = 300	Conde-Agudelo 2003 <sup>164</sup> Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	Ecuador
Rojas 2003 <sup>121</sup>	RCT <i>n</i> = 57	McInnes 2006 <sup>161</sup>	USA
Blaymore Bier 1996 <sup>115</sup>	RCT <i>n</i> = 41	McInnes 2006 <sup>161</sup>	USA
Roberts 2000 <sup>129</sup>	RCT <i>n</i> = 30	McInnes 2006 <sup>161</sup>	Australia
Kadam 2005 <sup>118</sup>	Pilot RCT <i>n</i> = 89	McInnes 2006 <sup>161</sup>	India
Hurst 1997 <sup>139</sup>	Before/after <i>n</i> = 23	McInnes 2006 <sup>161</sup>	USA
Wahlberg 1992 <sup>135</sup>	Before/after <i>n</i> = 66	McInnes 2006 <sup>161</sup>	Sweden
Wilhelm 2005 <sup>150</sup>	Crossover <i>n</i> = 25	No	USA
Whitelaw 1988 <sup>147</sup>	RCT <i>n</i> = 63	No	UK
Boo 2007 <sup>141</sup>	RCT <i>n</i> = 126	No	Malaysia

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

b Charpak 1997<sup>107</sup> and 2001<sup>108</sup> papers pertain to the same study.

comprised participants who were mostly high-level professionals<sup>115</sup> or on medium to high incomes.<sup>141</sup> Maternal participants in the trial performed in the UK were mostly white (*n* = 50/63, 79%) with small numbers of Asian and Afro-Caribbean participants.<sup>147</sup>

Two trials focused on mothers who intended to<sup>115</sup> or had started to<sup>118</sup> express breastmilk or

breastfeed their infants. Two further trials reported participants' intention to breastfeed<sup>147</sup> and exclusive breastfeeding behaviour at enrolment<sup>131</sup> by comparison groups.

#### **Characteristics of interventions**

Eight trials evaluated the skin-to-skin component of KMC where the infant is held upright between the mother's breasts in a nappy and hat, usually

**TABLE 3** Summary of characteristics of RCTs evaluating 'increased mother and infant contact'

Study	Country	Components of intervention	Total period of intervention	Duration of each daily contact	Inclusion criteria for infants by BW or GA	Other criteria for eligible infants
Boo 2007 <sup>141</sup>	Malaysia	Kangaroo skin-to-skin contact	Up to hospital discharge	1 hour	< 1500 g	Minimal ventilatory support
Kadam 2005 <sup>118</sup>	India	Kangaroo skin-to-skin contact	Up to hospital discharge	1 hour	< 1800 g	On oral feeds
Rojas 2003 <sup>121</sup>	USA	Kangaroo skin-to-skin contact	Up to hospital discharge	Up to 8 hours in two 4-hour periods	< 1500 g	Minimal ventilatory support
Roberts 2000 <sup>129</sup>	Australia	Kangaroo skin-to-skin contact	Up to hospital discharge	Not reported	≥ 30 weeks	On enteral feeds
Cattaneo 1998 <sup>131</sup>	Mexico	Kangaroo skin-to-skin contact	Up to 40th week postnatal age	20 hours	1000–1999 g	On enteral feeds
Blaymore Bier 1996 <sup>115</sup>	USA	Kangaroo skin-to-skin contact	10 days	10 minutes	< 1500 g	Gavage fed
Sloan 1994 <sup>132</sup>	Ecuador	Kangaroo skin-to-skin contact	Up to hospital discharge	Not reported	< 2000 g	On enteral feeds
Whitelaw 1988 <sup>147</sup>	UK	Kangaroo skin-to-skin contact	Up to and beyond hospital discharge	At hospital visits (mean 2.1 hours daily visiting)	< 1500 g	No oxygen equipment
Charpak 1997, 2001 <sup>107,108</sup>	Colombia	Kangaroo skin-to-skin contact; early hospital discharge; regular breastfeeding	Up to 41 weeks corrected age	24 hours	< 2000 g	Satisfactory suck and swallow reflex

covered by a blanket, and in a private setting, compared with traditional care where contact between mother and infant is fully clothed and privacy is not the norm.<sup>115,118,121,129,131,132,141,147</sup> The remaining trial evaluated a more comprehensive KMC intervention,<sup>107,108</sup> namely, skin-to-skin contact together with early hospital discharge and regular, but not exclusive, breastfeeding. As characteristics of these studies vary, they are summarised in *Table 3*.

The total period during which kangaroo skin-to-skin contact was promoted varied considerably across trials, and between participants within trials; however, data on this were not reported in two trials.<sup>129,132</sup> Four trials reported the mean period of skin-to-skin contact during the hospital stay as 4.6 (range 0–40),<sup>107,108</sup> 8.5 (SD 4.4),<sup>118</sup> 11 (range 2–85), 17 (range not available)<sup>141</sup> and 61 (SD 28)<sup>121</sup> days. Two trials reported the median period of kangaroo skin-to-skin contact during the hospital stay as 11 (range 2–85)<sup>131</sup> and 30 (range 5–83)<sup>147</sup> days.

The large ranges around the average further highlight the heterogeneity of the total periods of kangaroo skin-to-skin contact between participants within an intervention group. This can be attributed in part to the range of birthweights of infants included in each trial and the inverse relationship between birthweight and length of hospital stay and in part to the diverse criteria for hospital discharge between trials.

The duration of each kangaroo skin-to-skin contact also varied considerably between trials. Three trials evaluated 'short' individual periods of contact of 10 minutes per weekday<sup>115</sup> and one hour daily.<sup>118,141</sup> A further trial evaluated the promotion of kangaroo skin-to-skin contact at all visits during and beyond hospital stay,<sup>147</sup> reporting a mean of 2.1 hours visiting per day. Data on actual contact time is not reported.<sup>147</sup>

One trial evaluated a 'medium' level of skin-to-skin kangaroo care contact of up to 8 hours per day in

two 4-hour periods.<sup>121</sup> Prolonged periods of contact were evaluated in two trials, defined as 24 hours per day until no longer tolerated by infant<sup>107,108</sup> and reported as a mean of 20 hours per day during hospital stay.<sup>131</sup> Two trials did not define or report the duration of individual kangaroo skin-to-skin contacts.<sup>129,132</sup>

The detail of standard care provided in control groups was limited. Incubators were available in all trials with the exception of one of the three study sites in the multicentre trial:<sup>131</sup> standard care in Addis Ababa was open cribs in a warm room.<sup>131</sup> The Colombian trial specified visiting as restrictive for mothers in the control group<sup>107,108</sup> while the UK trial specified open visiting practice as standard care.<sup>147</sup> Clothing of infants while being cuddled or fed was reported as standard care for the four trials conducted in industrialised countries.<sup>115,121,129,147</sup>

### Outcome assessment

One RCT reported the initiation of breastfeeding or receiving expressed breastmilk<sup>141</sup> assessed between enrolment and hospital discharge. Another trial evaluated the timing of the initiation of breastfeeding<sup>118</sup> assessed by the infant's mean age in days when breastfeeding started.

Seven trials reported the duration of breastfeeding.<sup>107,108,115,121,129,131,141,147</sup> Two of these trials reported the duration of lactation where the mother, and not the infant, was the unit of allocation and analysis.<sup>115,147</sup> Exclusive rates of breastfeeding were reported in two trials.<sup>107,108,132</sup> One trial also evaluated the primary outcome of production of expressed breastmilk.<sup>115</sup> Interpretation of findings and further analysis are limited, however, due to lack of any numerical data to report this outcome (see *Table 26* in Appendix 4.1).

Assessments of duration of breastfeeding varied between studies and included the following: 40–41 weeks' corrected age,<sup>107,108</sup> hospital discharge,<sup>115,121,129,141</sup> 1 month after hospital discharge,<sup>115</sup> 6 weeks,<sup>129</sup> more than 6 weeks,<sup>147</sup> 3 months,<sup>107,108,129</sup> 6 months,<sup>107,108,129</sup> 9 months,<sup>107,108</sup> and 12 months<sup>107,108</sup> and mean weeks' lactation.<sup>147</sup> Exclusive breastfeeding was assessed at 40–41 weeks' corrected age,<sup>107,108</sup> at hospital discharge and 1 and 6 months.<sup>132</sup> With the exception of one trial,<sup>121</sup> it is not clear whether the measures of breastfeeding started at the point of non-nutritive or nutritive breastfeeding.

All nine RCTs reported data on secondary outcomes including health,<sup>107,108,115,118,121,129,131,132,141</sup> process,<sup>107,108,115,118,121,129,131,132,141,147</sup> psychosocial<sup>118,131,141</sup> and cost-effectiveness outcomes.<sup>108,109,131</sup>

One trial observed and monitored the predefined short duration of kangaroo skin-to-skin contact time.<sup>115</sup> This is unlikely to be possible for interventions promoting continuous or prolonged contact. The amount of enhanced kangaroo skin-to-skin contact is likely to be variable therefore between participants within each trial.

### Methodological quality of included trials

No trials were rated as 'good' quality overall. Eight trials were rated as 'moderate' quality.<sup>107,108,115,118,121,131,132,141,147</sup> The remaining trial was considered to be 'poor' quality.<sup>129</sup> Serious caution is warranted in interpretation of the results of this trial. Details of the quality ratings for each trial are provided in *Table 74* in Appendix 5.

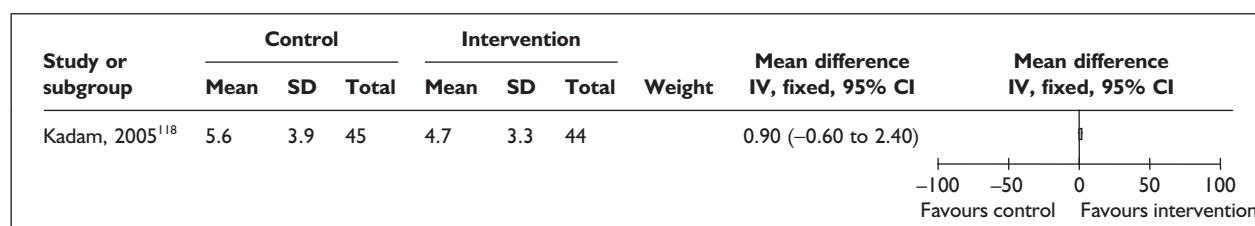
### Effectiveness of interventions

#### Primary outcomes

Complete outcome data for all those originally enrolled were provided in three trials,<sup>118,141,147</sup> including data for postrandomisation exclusions where appropriate.<sup>141</sup> Relevant data have been sought and/or extracted to perform intention-to-treat analysis using postrandomisation exclusion data for five trials.<sup>107,108,115,121,131,132</sup> It was not possible to estimate the relative risk for primary outcome data for one study due to lack of denominator data.<sup>129</sup>

Individual relative risk estimates for primary outcomes in trials that did not receive a poor overall quality rating are presented in forest plots.<sup>107,108,115,118,121,131,132,147</sup> These have been calculated on an ITT basis.

No trials evaluated the effect of mother and infant contact on the primary outcome of initiation of breastfeeding or oral feeding of expressed breastmilk. One small trial in India shows that kangaroo skin-to-skin contact for 1 hour a day has no effect on the age of initiation of breastfeeding among infants with birthweights of less than 1800 g<sup>118</sup> (*Figure 2*). Some caution in interpretation of findings is required as age of the infants at enrolment is not reported by comparison group and between-group differences may affect this outcome. All infants in this study received only human milk and were either breastfed or spoon-fed.



**FIGURE 2** Kangaroo skin-to-skin contact vs standard care: age at initiation of breastfeeding (ITT).

Two trials that evaluated the effect of kangaroo skin-to-skin contact on the duration of any breastfeeding before hospital discharge in industrialised settings showed a positive effect of the intervention compared with standard care<sup>121,141</sup> (Figure 3). Both trials were conducted among infants of very low birth weight and among populations with typically low breastfeeding rates (30% in 2000 census of study neonatal unit<sup>141</sup> and 74% initiation in the USA nationally.<sup>165</sup>

Results from one large trial have shown a statistically significant between-group difference ( $p = 0.004$ ) as a result of the intervention.<sup>141</sup> This trial promoted kangaroo skin-to-skin contact for 1 hour a day with a mean hospital stay of 17 days (no range available). Some caution is required in interpretation of these findings as infants in the intervention group were of significantly later postmenstrual age, and intervention mothers had significantly more years of education, than their respective control groups.<sup>141</sup>

A US-based trial reported no effect of the intervention. Findings of this trial are based on samples that are underpowered both as a total and as a subgroup sample for each comparison group and are not conducted on an ITT basis,<sup>121</sup> and compliance was low in both groups.

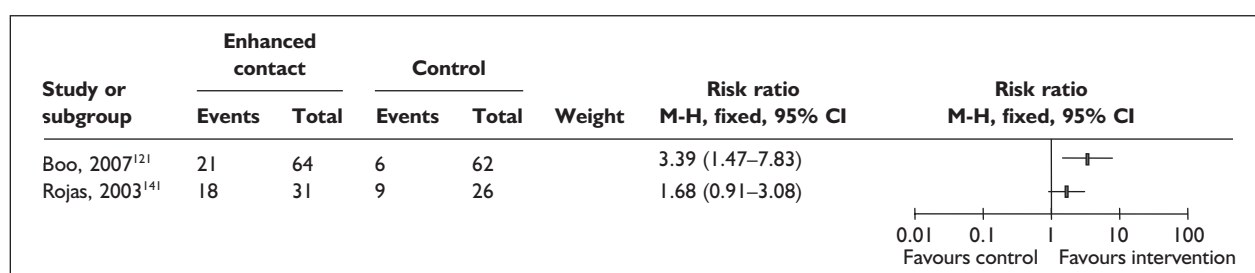
Two trials that evaluated the effect of kangaroo skin-to-skin contact on the duration of any

breastfeeding at hospital discharge showed a statistically significant increase ( $p = 0.05$ , Boo *et al.*, 2007;<sup>141</sup>  $p = 0.02$ , Blaymore Bier *et al.*, 1996<sup>115</sup>) in favour of the intervention compared with standard care (Figure 4). As stated above, some caution is required in interpretation of findings from this trial.<sup>141</sup>

Two trials<sup>115,141</sup> were conducted among infants of very low birthweight and among populations with low breastfeeding rates (as detailed above). Kangaroo skin-to-skin contact was for short periods in both trials, comprising 10 minutes per day for 10 days<sup>115</sup> and 1 hour daily during a mean hospital stay of 17 days (no SD available).<sup>141</sup>

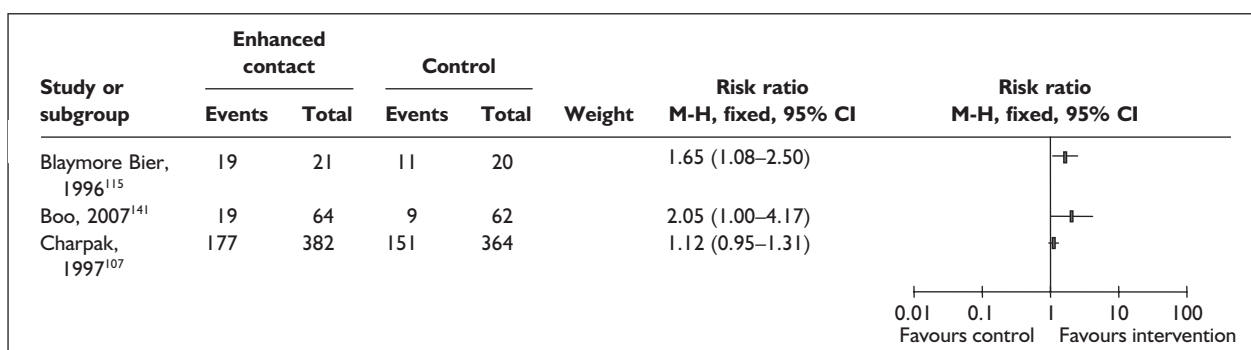
One large trial evaluated a comprehensive intervention of KMC comprising prolonged kangaroo skin-to-skin contact, early discharge and regular breastfeeding.<sup>107</sup> No positive effect was found for duration rates of any breastfeeding at 40–41 weeks corrected age among infants of low birthweight in this resource-poor country setting.

Two small, moderate-quality trials evaluated the effect of kangaroo skin-to-skin contact on the duration of any breastfeeding for prolonged periods (more than 6 weeks;<sup>147</sup> and 1 month after discharge<sup>115</sup>). Both trials took place in industrialised settings and demonstrated a statistically significant effect in favour of the intervention compared with standard care



**FIGURE 3** Kangaroo skin-to-skin contact vs standard care: duration of any breastfeeding before hospital discharge (ITT).





**FIGURE 4** Kangaroo mother care vs standard care: duration of any breastfeeding at hospital discharge or 40–41 weeks corrected age (ITT).

( $p = 0.01$ , Blaymore Bier *et al.*, 1996;<sup>115</sup>  $p = 0.04$  Whitelaw *et al.*, 1988<sup>147</sup>) (Figure 5). These interventions comprised relatively short daily periods of kangaroo skin-to-skin contact among infants of very low birthweight. Most of the mothers participating in the UK-based trial intended to breastfeed<sup>147</sup> and all women in the US-based trial were expressing milk and planning to breastfeed.<sup>115</sup>

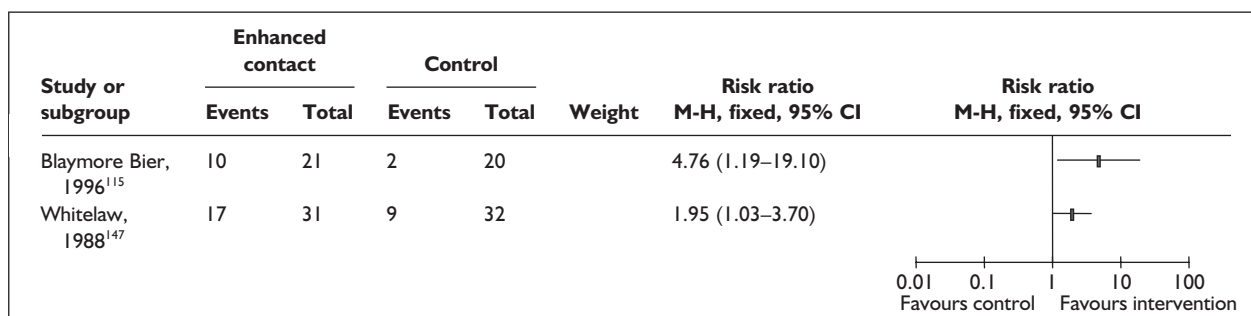
Significantly increased rates of any breastfeeding at 1 and 3 months corrected age were also reported as a result of a comprehensive kangaroo mother care intervention.<sup>108</sup> These findings are not based on an ITT analysis and outcome data are reported as percentages only.<sup>108</sup> These results are not presented in Figure 5.

Three trials evaluated the effect of kangaroo skin-to-skin contact on exclusive breastfeeding rates in resource-poor country settings.<sup>107,108,131,132</sup> A multicentred trial was conducted at three sites in three continents.<sup>131</sup> Results for each site have been presented separately to reflect between-site differences in characteristics of participants and standard care for control groups (Figure 6).

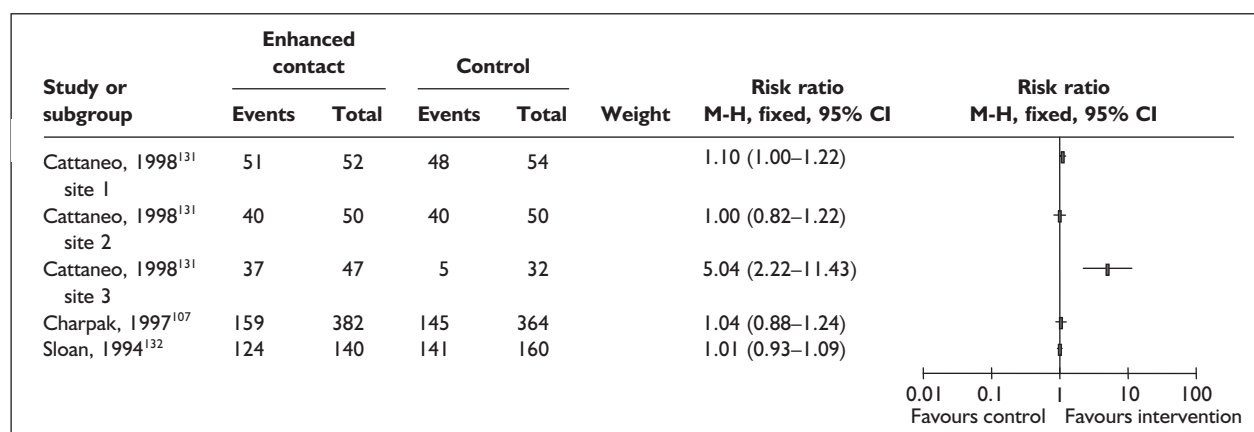
With the exception of one site in the multicentred trial, kangaroo skin-to-skin contact has been shown to have no effect on the duration of exclusive breastfeeding at hospital discharge or 40–41 weeks corrected age among infants of mainly low birthweight in resource-poor country settings (see Figure 6). Cattaneo *et al.* (1998)<sup>131</sup> reported that exclusive breastfeeding rates at enrolment were significantly lower at the site that demonstrated a positive effect as a result of the intervention compared with sites one and two ( $p = 0.003$ ). The differences in characteristics of participants, organisational and country setting and standard care between the three sites limit the ability to interpret the potential factors influencing the different findings reported for this site.

One trial (Sloan *et al.*, 1994) also found that exclusive breastfeeding rates favoured the control group at 1 and 6 months.<sup>132</sup>

Two of these trials were large, with a total of 300<sup>132</sup> and 777<sup>107,108</sup> participants across two arms in each trial. The three sites in the multicentre trial were of moderate size ( $n = 100, 104, 79$ , respectively) although an a priori sample size calculation



**FIGURE 5** Kangaroo skin-to-skin contact vs standard care: duration of any breastfeeding for prolonged periods (ITT).



**FIGURE 6** Kangaroo skin-to-skin contact vs standard care: duration of exclusive breastfeeding at hospital discharge or 40–41 weeks corrected age.

had not been made.<sup>131</sup> The moderate quality of these larger trials, including between-group comparability at baseline, suggests these findings can be interpreted with some confidence. These trials suggest therefore that kangaroo skin-to-skin contact is not likely to increase the duration of exclusive breastfeeding rates at or beyond hospital discharge among mainly low birthweight infants in resource-poor country settings.

### Secondary outcomes

Results for secondary outcomes are taken from available study data, including ITT analysis where available.

Two trials conducted among infants of very low birthweight and that employed ITT analysis for clinical outcome data reported a significantly greater mean weekly increase in head circumference (measured in centimetres) for the intervention group [intervention (I): 1.0 (SD 0.3); control (C): 0.7 (SD 0.3);  $p < 0.0001$ ]<sup>141</sup> and significantly greater rate of head growth (cm/day) (SD) for infants in intervention than control groups [I: 0.1 (0.03); C: 0.08 (0.02);  $p < 0.05$ ].<sup>121</sup> The third trial did not report raw data or conduct ITT analysis for health outcomes among study infants with a birthweight of 2000 g or less.<sup>108</sup> This study reported infants in the intervention group having a larger head circumference than control group infants at 12 months after estimated term ( $p = 0.0014$ ).<sup>108</sup>

Intention-to-treat analysis was employed by two small trials, which reported favourable outcomes for levels of oxygen saturation in the intervention groups.<sup>118,121</sup> Rojas *et al.* (2003)<sup>121</sup> reported a

significantly lower incidence of desaturation among very low birthweight infants in the intervention group than in the control group (I: 10/33; C: 15/27;  $p = 0.05$ ). Mean oxygen saturation was found to be significantly higher for intervention than control groups (I:  $95.7 \pm 1.1$ ; C:  $94.8 \pm 0.7$ ;  $p < 0.01$ ) and respiratory rates were significantly lower for the intervention group (I:  $36.2 \pm 3.3$ ; C:  $40.7 \pm 2.9$ ;  $p < 0.01$ ).<sup>118</sup> One very small trial conducted in the USA among infants of very low birthweight found mean oxygen saturation was higher for intervention than for control groups ( $p < 0.001$ ), with falls in haemoglobin oxygen saturation to  $< 90\%$  occurring in 191/1716 (11%) recordings during skin-to-skin contact compared with 319/1334 (24%) during standard care ( $p < 0.001$ ).<sup>115</sup> This study did not employ ITT analysis for assessment of clinical outcomes although losses to study were small (I: 0; C: 2).<sup>115</sup>

Episodes of hypothermia (per 100 infants/day) were lower in one multicentred trial (I: 213 (10.8); C: 325 (14.6);  $p = 0.0005$ ), particularly at the Mexican site (I: 82 (13.5); C: 141 (31.5);  $p = 0.00001$ ).<sup>131</sup> These data were analysed on an available-case basis. A small trial that employed ITT analysis also reported fewer episodes of hypothermia in the intervention than in the control group (I: 10/44; C: 21/45;  $p < 0.01$ ).<sup>118</sup> Both trials were conducted mainly among infants of low birthweight.<sup>118,131</sup>

A trial conducted in Ecuador among low birthweight infants<sup>132</sup> reported significant between-group differences for serious morbidity at 2 months (I: 7/131; C: 27/152;  $p = 0.002$ ) and 6 months ( $p = 0.005$ ). The difference at 2 months reduced slightly ( $p = 0.007$ ) when controlled for pre-

eligibility differences.<sup>132</sup> No significant differences were found between comparison groups for mild or moderate disorders.<sup>132</sup> These findings are not based on an ITT analysis although losses to study were less than 20% and the overall sample size was relatively large ( $n = 300$ ).

No significant differences were found between comparison groups for incidence of sepsis,<sup>118,121,131,141</sup> necrotising enterocolitis (NEC),<sup>118,121,131,141</sup> apnoea,<sup>118</sup> hyperthermia<sup>118</sup> or growth indices including daily weight gain,<sup>132,141</sup> weight at discharge,<sup>118</sup> mean head circumference,<sup>141</sup> total weight gain, total head circumference growth, total linear growth, rate of weight gain or rate of linear growth.<sup>121</sup>

Process outcomes including median age at discharge, mean postmenstrual age at discharge<sup>141</sup> and length of hospital stay<sup>118,121</sup> were reported to be similar between comparison groups.

The one trial that evaluated a more comprehensive kangaroo mother care intervention including prolonged upright skin-to-skin contact, regular breastfeeding and early discharge found no differences between comparison groups for mortality or infectious morbidity, numbers of readmissions after discharge and psychomotor development up to 12 months.<sup>107,108</sup> These data were analysed on an available-case basis although losses to study were less than 20% and the overall sample size was large ( $n = 777$ ).

A trial that evaluated mothers' views of the intervention conducted among mothers of low birthweight infants in India reported that 86% of mothers were happy with kangaroo skin-to-skin contact and 14% preferred conventional care.<sup>118</sup> A UK-based study including very low birthweight infants<sup>147</sup> found no significant differences between groups for levels of maternal self-reported confidence and positive feelings towards the infant at discharge and at age 6 months. One trial conducted in Malaysia examined mothers' reasons for non-compliance with kangaroo skin-to-skin contact.<sup>141</sup> Reasons cited included mothers' fear of handling their very low birthweight infants, mothers unable to visit regularly and fear that skin-to-skin contact would prevent their infant gaining weight.<sup>141</sup>

Two trials that conducted a cost analysis of the intervention compared with standard neonatal care were conducted in resource-poor country settings

among mainly low birthweight infants.<sup>131,132</sup> Both trials reported kangaroo skin-to-skin contact as less expensive overall than standardised incubator care, which was quantified in one study as \$340 higher.<sup>132</sup> Both trials noted specific higher costs associated with the intervention including food for mothers and laundry<sup>131</sup> and costs associated with increased contact time between mother, infant and siblings in the clinic.<sup>132</sup> Increased contact time was noted also to achieve improved capacity of mothers to care for their infants.<sup>132</sup>

No adverse effects were reported as a result of kangaroo skin-to-skin contact, with or without early discharge from hospital, for infants of low or very low birthweight, when compared with standard care.

## Results from other study designs

Three other forms of controlled studies were identified (*Tables 35–37* in Appendix 4.1).<sup>135,139,150</sup> These include one repeated measures, crossover design<sup>150</sup> and two cross-sectional before/after studies.<sup>135,139</sup> One before/after study collected retrospective data for the control group,<sup>139</sup> the other for both comparison groups.<sup>135</sup>

### Characteristics of participants

All three studies were conducted in industrialised countries, including two in the USA<sup>139,150</sup> and one in Sweden.<sup>135</sup> One study recruited all mothers in the neonatal unit, before and after introduction of a skin-to-skin holding policy in the neonatal unit.<sup>139</sup> It appears that all infants in the neonatal unit were ventilated and low birthweight.<sup>139</sup> Two studies included mother–infant pairs with stable infants according to predefined inclusion criteria: one study included infants aged 1–30 days when first taken out of the incubator,<sup>135</sup> and another study included mothers of infants born < 33 weeks' gestation and/or birthweight < 2000 g.<sup>150</sup> In this study, infants participated in the intervention during their first week of life and were not expected to breastfeed during the study period.<sup>150</sup> The study also recruited mothers who were already expressing breastmilk and intended to breastfeed for at least 3 months.<sup>150</sup> Maternal characteristics indicate these women were mostly white, not on very low incomes and held private insurance.<sup>150</sup>

All infants included in these studies were preterm, gestational age ranging from a mean of 28 weeks<sup>150</sup> to a mean of 32 weeks<sup>150</sup>. Mean birthweights were reported as 1490 g,<sup>135</sup> 1092 g<sup>139</sup> and 1652 g.<sup>150</sup>

### Characteristics of interventions

All three studies evaluated skin-to-skin mother and infant contact.<sup>135,139,150</sup>

One study defined the skin-to-skin component of kangaroo mother care with chest-to-chest contact for 1 hour of either 1 or 2 days depending on the comparison group within the first week of the infant's life.<sup>150</sup> Mothers in the control group had no kangaroo care contact with unlimited visiting of their infant at the cotside.<sup>150</sup>

Two studies promoted undefined skin-to-skin contact for either 30 minutes daily over a 2-week period compared with undefined standard care<sup>139</sup> or as much as mother desired until hospital discharge, compared with mothers holding infants dressed and with blanket or heating pad.<sup>135</sup>

### Outcome assessment

One study reported the effect of kangaroo skin-to-skin contact on breastmilk production at 4–6 days<sup>150</sup> and another reported the effect of skin-to-skin contact on the duration of breastfeeding at hospital discharge.<sup>135</sup> The remaining study reported breastmilk volume at 2, 3 and 4 weeks and rates of any and exclusive breastfeeding after hospital discharge.<sup>139</sup>

### Methodological quality of included studies

One study was rated as 'moderate' quality (Wahlberg *et al.*, 1992<sup>135</sup>), with some criteria being fulfilled, and where they were not met, the study conclusions are thought unlikely to alter.

Two studies were rated as 'poor' quality (Wilhelm, 2005;<sup>150</sup> Hurst *et al.*, 1997<sup>139</sup>), in which few criteria were fulfilled and the conclusions of the study are thought very likely to alter.

Details of the quality ratings for each study are provided in *Tables 75* and *76* in Appendix 5.

### Effectiveness of interventions

#### Primary outcomes

It is not clear how outcome data have been derived and compared between comparison groups in the crossover study.<sup>150</sup> This limitation warrants extreme caution in interpretation of findings, and results have not been presented for this study. Some caution is warranted in interpretation of findings from the remaining studies due to methodological limitations of the study designs.<sup>135,139</sup>

Wahlberg *et al.* (1992)<sup>135</sup> report a retrospective comparison of records from a convenience sample

of 66 mothers and infants in Sweden, half from the 18 months before the introduction of skin-to-skin contact and half from the 18 months following its introduction. The mothers and infants were well matched, but no comparisons with the population of mothers and infants in the unit are reported. This study reports higher rates of breastfeeding at hospital discharge [before (B): 15/33; after (A): 27/33; *p* value not reported in paper, calculated on an ITT basis *p* = 0.005].

The before/after study conducted in the USA reported a substantial increase in milk volume (ml) at 2 weeks for mothers in the 'after' group exposed to skin-to-skin contact compared with mothers in the non-exposed 'before' group (B: 462, SD 222; A: 574, SD 211).<sup>139</sup> The greater milk volume was maintained at 4 weeks (B: 421, SD 315; A: 851, SD 259) with the pattern of milk volume between groups from weeks 2 to 4 reported as significantly different (*p* = 0.01).

### Secondary outcomes

One before/after study<sup>135</sup> reported that infants in the exposed 'after' group were younger when they first came out of the incubator (*p* < 0.01), gained more weight per week (*p* < 0.05) and spent fewer days in the incubator (*p* < 0.05) and in hospital (*p* < 0.05). Authors note the methodological limitations of this study and the lack of generalisability of findings.<sup>135</sup>

No lasting adverse incidents during skin-to-skin contact were reported in one before/after study.<sup>139</sup> Authors report the occurrence of an episode of mild oxygen desaturation in two infants exposed to the intervention.<sup>139</sup>

## Interim feeding methods and related interventions

A total of six primary studies and three systematic reviews examining interim feeding methods and related interventions were identified. As detailed in *Table 4*, all primary studies were included in at least one of three previous systematic reviews. All but one<sup>122</sup> were conducted in industrialised country settings, including two in the UK.<sup>120,124</sup>

## Results from randomised controlled trials

Five RCTs of interim feeding methods and related interventions were identified<sup>119,120,122,124,130</sup> (*Tables 38–42* in Appendix 4.1).

**TABLE 4** Included studies for 'Interim feeding methods and related interventions'

Primary paper	Study design (n analysed) <sup>a</sup>	Inclusion in existing systematic review	Country
Collins 2004 <sup>119</sup>	RCT (n = 303)	Edmond 2006 <sup>155</sup> Flint 2007 <sup>163</sup> McInnes 2006 <sup>161</sup>	Australia
Gilks 2004 <sup>120</sup>	RCT (n = 40)	Flint 2007 <sup>163</sup> McInnes 2006 <sup>161</sup>	UK
Kliethermes 1999 <sup>130</sup>	RCT (n = 84)	McInnes 2006 <sup>161</sup>	US
Meier 2000 <sup>136</sup>	Retrospective crossover study (n = 34)	McInnes 2006 <sup>161</sup>	US
Mosley 2001 <sup>124</sup>	RCT (n = 16)	Flint 2007 <sup>163</sup> McInnes 2006 <sup>161</sup>	UK
Rocha 2002 <sup>122</sup>	RCT (n = 78)	Edmond 2006 <sup>155</sup> Flint 2007 <sup>163</sup> McInnes 2006 <sup>161</sup>	Brazil

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

### Characteristics of participants

Four trials were conducted in industrialised country settings including two in the UK,<sup>120,124</sup> one in the USA<sup>130</sup> and one in Australia.<sup>119</sup> The fifth trial was conducted in Brazil.<sup>122</sup>

All trials recruited infants in neonatal units using criteria of birthweight and/or gestational age at birth or study entry. Inclusion criteria comprised varying combinations of birthweight and gestational age: singleton or twin infants of less than 34 weeks' gestation in Collins *et al.* (2004);<sup>119</sup> over 30 weeks' at time of study entry and up to 35 weeks' gestation at birth in Gilks and Watkinson (2004);<sup>120</sup> 'preterm' infants of 1000–2500 g in Kliethermes *et al.* (1999);<sup>130</sup> 30–37 weeks' gestation in Mosley *et al.* (2001);<sup>124</sup> and 32–36 weeks' gestation and weighing less than 1700 g in Rocha *et al.* (2002).<sup>122</sup>

All trials excluded infants with congenital abnormality that precluded enteral feeding. In addition, a variety of entry criteria were used that indicated that infants unable to tolerate enteral feeds would be excluded.

All trials were restricted to mothers who were breastfeeding or were planning to breastfeed.

Limited information on socioeconomic or ethnic background of the mothers was given. The study of Kliethermes *et al.* (1999)<sup>130</sup> was conducted in a private regional perinatal centre, probably indicating that poor women were unlikely to be included. Rocha *et al.* (2002)<sup>122</sup> reported that in their trial in Brazil, over 60% had incomplete primary schooling and 70% were on a low annual income.

### Breastfeeding rates in population

Background breastfeeding rates in the population groups from which these studies drew varied. Collins *et al.* (2004)<sup>119</sup> noted that 85% of women in Australia started to breastfeed at that time, and the rate in their study unit was 45%. Gilks and Watkinson (2004)<sup>120</sup> noted that 65% of women in their region of the UK started to breastfeed, and 40% of women in their study unit. Rocha *et al.* (2002)<sup>122</sup> noted that only 20% of mothers of infants born weighing less than 1500 g breastfed at 3 months, although the population prevalence in Brazil is likely to be higher than in the UK. Neither Kliethermes *et al.* (1999)<sup>130</sup> nor Mosley *et al.* (2001)<sup>124</sup> gave information about breastfeeding rates in their populations, although it is likely that the rates for Mosley *et al.* (2001)<sup>124</sup> are comparable with Gilks and Watkinson (2004).<sup>120</sup>

### Characteristics of interventions

Four trials examined the giving of oral enteral feeds by cup versus bottle.<sup>119,120,122,124</sup> One studied the use of a nasogastric tube versus bottle.<sup>130</sup> Two trials also examined the use of pacifiers as a co-intervention.<sup>119,122</sup> In one of these trials<sup>119</sup> the use of pacifiers was randomised in a 2×2 design. In Rocha *et al.* (2002),<sup>122</sup> the cup-feeding group also had pacifiers withdrawn and ‘non-nutritive sucking was provided by offering the little finger’. The implication is that the bottle-feeding group had pacifiers offered as part of standard care.

Although not explicitly stated, the implication in these trials was that the intervention continued until the infant was able to breastfeed exclusively, or as a means of complementary feeding once breastfeeding was established.

In all studies, it appeared that bottle feeding, and nasogastric tube feeding when it occurred, were standard care with which staff were familiar, with cup feeding being a novel or recently introduced technique.

#### Cup feeding

Use of, and staff training for, cup feeding varied between studies. In two studies, staff were trained in cup feeding before the trial started; Gilks and Watkinson (2004)<sup>120</sup> indicated that it had been introduced to the unit 6 months before the start of the trial and supported by a teaching programme, and Rocha *et al.* (2002)<sup>122</sup> indicated that staff were trained as part of a prior pilot project. Two other studies introduced cup feeding only in the context of and at the time of the trial; in Collins *et al.* (2004)<sup>119</sup> participating hospitals received education, written instructions, and one-to-one support during the trial, and Mosley *et al.* (2001)<sup>124</sup> reported that they gave an information sheet to all staff.

Rocha *et al.* (2002)<sup>122</sup> described the technique of cup feeding; the infant was held in a slightly inclined position, having the cup touch the lower lip, allowing the infant to lick or sip the milk and avoiding pouring the milk into the child’s mouth. The cup they used was the protective cap of a feeding bottle. Collins *et al.*<sup>119</sup> noted that milk feeds were given via a small plastic medicine cup. In both of these trials, cup feeds were given when the mother was unable to breastfeed or additional milk was required after a breastfeed. Mosley *et al.* (2001)<sup>124</sup> and Gilks and Watkinson (2004)<sup>120</sup> do not describe the technique used.

The type of milk given by cup or bottle was not specified in Collins *et al.* (2004).<sup>119</sup> In the other studies, the milk used was expressed breastmilk.

#### Bottle feeding

No description of this technique is given, so no information is available on the type of teat or bottle used, the feeding technique used, or staff training.

#### Nasogastric tube feeding

This intervention involved the use of an indwelling nasogastric tube as an alternative to bottle feeding.<sup>130</sup> If a tube was already in place in infants allocated to the bottle-feeding group, it was removed ‘at the clinician’s discretion’.

#### Pacifiers

No study examined the use of pacifiers alone; they were used only as co-interventions. No information about the type of pacifier used in either study<sup>119,122</sup> is available. Pacifiers were used during tube feeds, or when the infant was restless.<sup>119</sup> It was noted that in the group that did not receive pacifiers in Rocha *et al.* (2002)<sup>122</sup> ‘non-nutritive sucking was provided by offering the little finger’, which in itself is an alternative intervention to the use of pacifiers. No information is provided, however, on the use of either pacifiers or fingers for non-nutritive sucking in either group.

#### Compliance

Only Collins *et al.* (2004)<sup>119</sup> gave details of compliance rates. They were low; 56% of infants randomised to cup feeding had a bottle introduced, and 31% of those randomised to ‘no pacifier’ had one. It was noted that the hospital with the best compliance had used cup feeding before.

Collins *et al.*<sup>119</sup> reported a total of 16 exclusions, 10 from the cup-feeding group and 6 from the bottle-feeding group as a result of the mother’s decision or infant death. Gilks and Watkinson<sup>120</sup> reported a differential withdrawal rate between their groups: 41% of mothers withdrew from the cup-feeding group, while only 11% withdrew from the bottle-feeding group. Reasons given were that mothers no longer wished to breastfeed or infants became ill or were on medication that contraindicated breastfeeding. Kliethermes *et al.* (1999)<sup>130</sup> noted that six infants withdrew from the bottle-fed group and nine from the nasogastric tube group. Mosley *et al.*<sup>124</sup> noted two exclusions from the cup-feeding group. Three infants were excluded from the cup-feeding group and two from the bottle-feeding group in Rocha *et al.*;<sup>122</sup> reasons are given.

### Outcome assessment

All studies examined breastfeeding duration, although reported it in different ways. Any breastfeeding at discharge was reported by all trials, and exclusive breastfeeding at discharge was also reported by Collins *et al.* (2004),<sup>119</sup> Gilks and Watkinson (2004),<sup>120</sup> Kliethermes *et al.* (1999)<sup>130</sup> and Mosley *et al.* (2001).<sup>124</sup>

Gilks and Watkinson<sup>120</sup> reported exclusive and any breastfeeding rates at the equivalent of term and 6 weeks post-term gestational ages. Kliethermes *et al.*<sup>130</sup> reported age at first breastfeeding, and exclusive and any breastfeeding rates at 3 days post discharge. Rocha *et al.*<sup>122</sup> reported any breastfeeding rates at 5–15 days post follow-up, at 3 months and after 3 months. Collins *et al.*<sup>119</sup> and Kliethermes *et al.*<sup>130</sup> reported any breastfeeding at 3 and 6 months after discharge, and Kliethermes *et al.*<sup>130</sup> also reported exclusive breastfeeding at 3 months after discharge.

A range of other outcomes were reported including: length of stay and adverse events;<sup>119</sup> time of nasogastric tube withdrawal;<sup>120</sup> side effects of tube feeding;<sup>130</sup> weight gain in the first week, time spent administering milk, and oxygen saturation.<sup>122</sup>

Psychosocial and cost outcomes were not reported.

### Methodological quality of included trials

Only one trial was rated as 'good' quality overall.<sup>119</sup> Compliance rates in this trial were low, however, which is likely to affect the results of the study.

Two trials were rated as 'moderate' quality.<sup>122,124</sup> Mosley *et al.* (2001)<sup>124</sup> is a very small ( $n = 14$ ) pilot study.

The remaining two trials were rated as 'poor' quality.<sup>120,130</sup> Serious caution is warranted in interpretation of the results of these trials. Details of the quality ratings for each trial are provided in Table 77 in Appendix 5.

### Effectiveness of interventions

#### Primary outcomes

Relevant data have been extracted to perform ITT analyses for four trials.<sup>119,120,122,124</sup> It was not possible to conduct ITT analyses on the remaining trial.<sup>130</sup>

Individual relative risk estimates, calculated on an ITT basis, are presented in forest plots for primary outcomes in the three trials that did not receive a poor overall quality rating.<sup>119,122,124</sup>

No trials evaluated the effect of feeding methods on the primary outcome of initiation of breastfeeding.

#### Cup feeding vs bottle feeding

No trials reported primary outcomes before the point of discharge.

Three trials gave results for the outcome of any breastfeeding at discharge.<sup>119,120,122</sup> None found a difference between the groups. Care is needed in interpreting this finding as rates of non-compliance were very high in Collins *et al.* (2004),<sup>119</sup> the only trial whose design was rated as good quality (Figure 7).

Three trials reported exclusive breastfeeding at discharge.<sup>119,120,124</sup> Mosley *et al.*<sup>124</sup> found no difference between the groups in their small pilot trial. Gilks and Watkinson<sup>120</sup> found that 10/27 (37%) in the cup-feeding group were exclusively breastfeeding, versus 4/27 in the bottle-feeding group (15%). In the only good-quality trial, Collins *et al.*<sup>119</sup> found an increase in exclusive breastfeeding in the cup-feeding group [relative risk (RR) 1.29; confidence interval (CI) 1.04–1.59]. Care is needed in interpreting this finding as rates of non-compliance were very high<sup>119</sup> (Figure 8).

#### Breastfeeding after discharge

There were no differences in any breastfeeding after discharge when measured at term and 6 weeks post term,<sup>120</sup> or at 5–15 days,<sup>122</sup> 3 months,<sup>119,122</sup> or 6 months<sup>119</sup> post discharge (Figures 9–11).

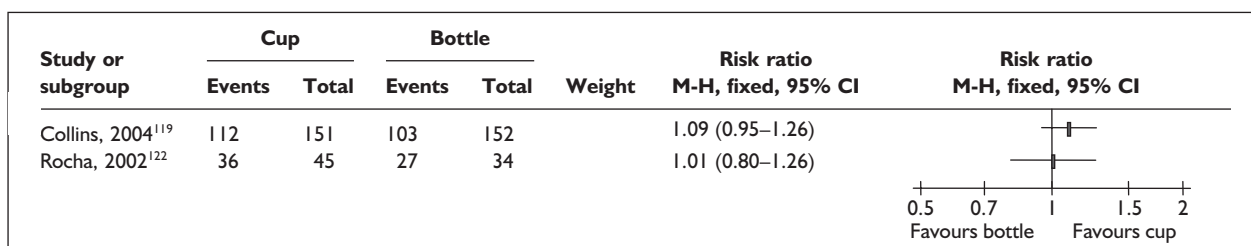


FIGURE 7 Cup feeding vs bottle feeding: any breastfeeding at discharge (ITT).

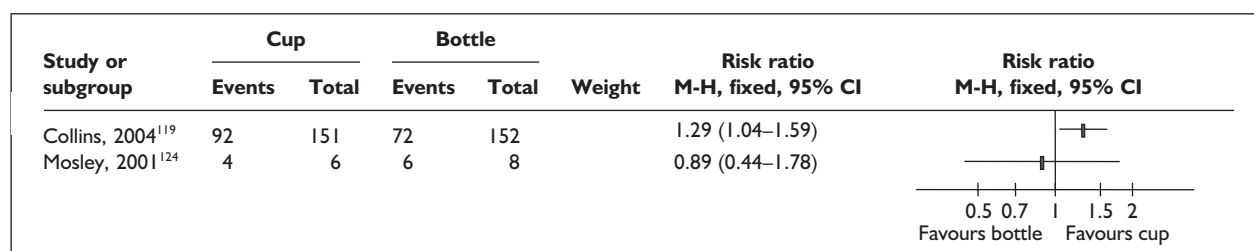


FIGURE 8 Cup feeding vs bottle feeding: exclusive breastfeeding at discharge (ITT).

**Nasogastric tube feeding vs bottle feeding**

Only one trial, rated as poor quality, examined the use of nasogastric feeding as an alternative to bottle feeding.<sup>130</sup> It was not possible to report ITT results due to the way in which data were reported.

**Pacifier use**

Two trials included pacifier use as part of the intervention,<sup>119,122</sup> but results are only reported separately from feeding method by Collins *et al.*<sup>119</sup>

No differences are reported in any or exclusive breastfeeding at discharge, or any breastfeeding

at 3 and 6 months after discharge (Figures 12–15). Compliance was an important issue to consider; 31% of infants randomised to the ‘no pacifier’ group received one.

**Secondary outcomes**

**Cup feeding vs bottle feeding**

Collins *et al.* (2004)<sup>119</sup> reported that length of stay was significantly increased in infants who were cup fed ( $p = 0.01$ ). This finding was confounded both by the fact that infants in the cup-feeding group took longer to satisfy the hospital criterion for discharge of taking all sucking feeds, and by the poor

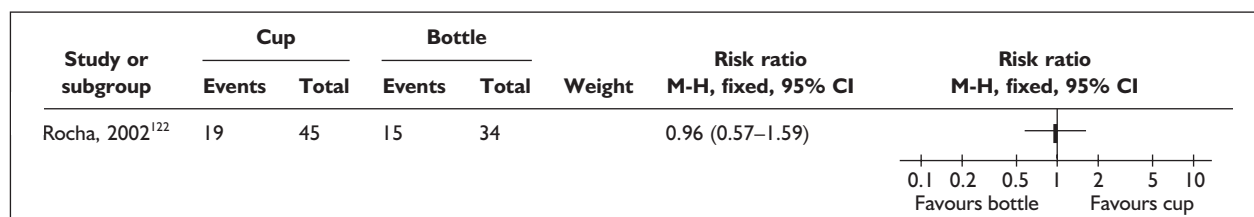


FIGURE 9 Cup feeding vs bottle feeding: any breastfeeding 5–15 days after discharge (ITT).



FIGURE 10 Cup feeding vs bottle feeding: any breastfeeding 3 months after discharge (ITT).

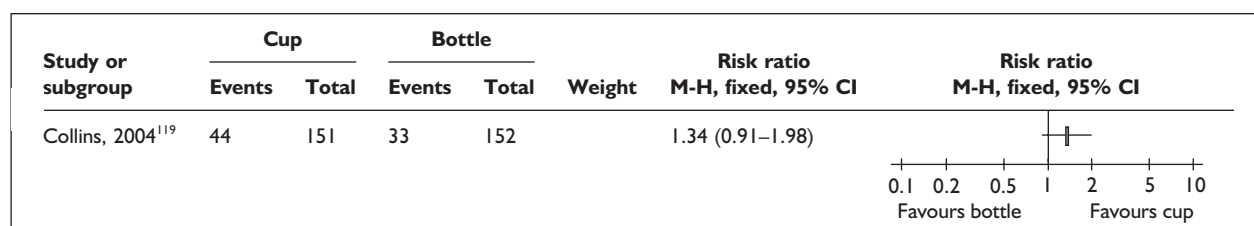


FIGURE 11 Cup feeding vs bottle feeding: any breastfeeding at 6 months after discharge (ITT).



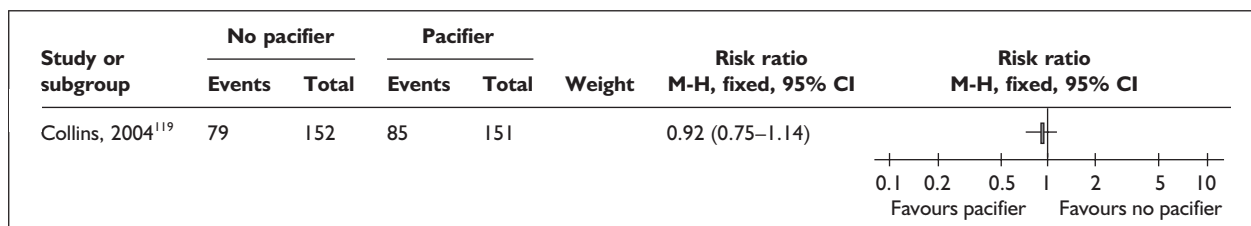


FIGURE 12 Pacifier use: fully breastfeeding at discharge (ITT).

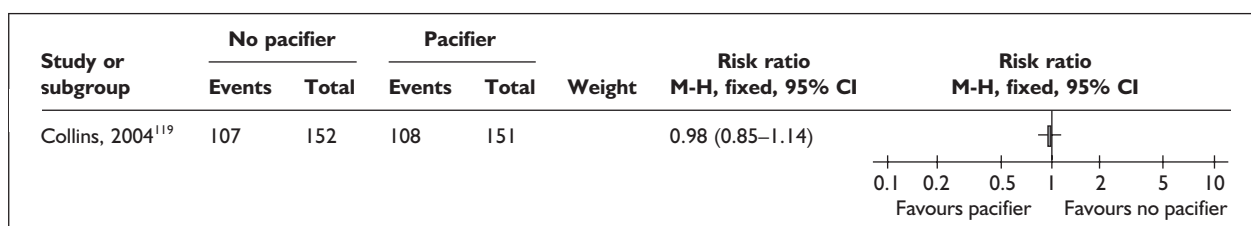


FIGURE 13 Pacifier use: any breastfeeding at discharge (ITT).

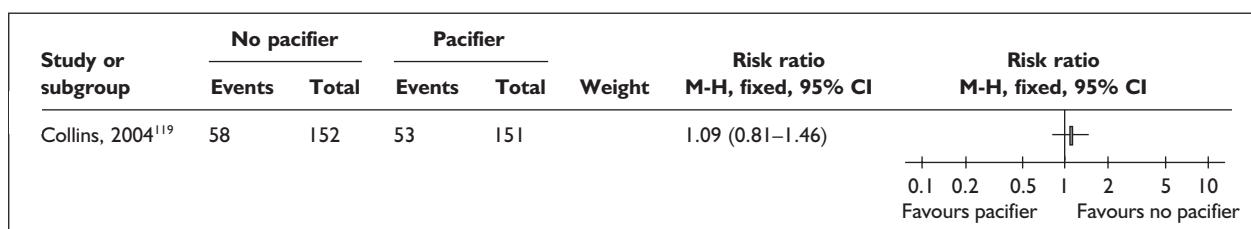


FIGURE 14 Pacifier use: any breastfeeding at 3 months after discharge (ITT).

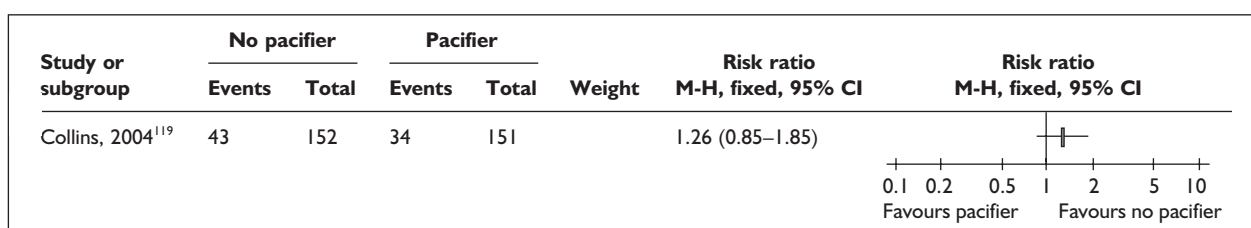


FIGURE 15 Pacifier use: any breastfeeding at 6 months after discharge (ITT).

compliance rates. It was noted that the hospital with the best compliance had used cup feeding before. Some staff had strong feelings against cup feeding and the withholding of pacifiers and some parents did not like cup feeding.

No differences were reported in mean weight gain and time administering milk between the two groups in Rocha *et al.* (2002).<sup>122</sup> These authors did

report a difference in severe oxygen desaturation (defined as < 85% during feeding: 35.3% in the bottle-fed group versus 13.6% in the cup-fed group,  $p = 0.02$ ). Gilks and Watkinson (2004)<sup>120</sup> reported no difference in time to withdrawal of the nasogastric tube, and Collins *et al.* (2004)<sup>119</sup> reported no difference in occurrence of adverse events including incidence of NEC.

**Pacifiers**

No difference in length of stay was found related to use of pacifiers,<sup>119</sup> but poor compliance remains an important issue.

**Results from other study types**

A study was identified concerning the use of ultra-thin silicone nipple shields for mother–infant pairs experiencing problems with breastfeeding, using a crossover design with retrospective analysis of data<sup>136</sup> (Table 43 in Appendix 4.1).

**Characteristics of participants**

Participants were mothers of preterm infants and their infants, already recruited to two trials of breastfeeding interventions. The 34 mother–infant pairs (14 infants were multiples, hence there were more infants than mothers) in the experimental groups in the trials, who experienced problems with attachment, sleepy infant and nipple pain, were included in this study. Mean birthweight (SD) was 1702 (521) g, mean weight at first breastfeeding (SD) was 1782 (403) g, gestational age at birth (SD) was 31.9 (3.0) weeks, and 70% were white, non-Hispanic ethnicity. No information is provided for breastfeeding rates in the population.

**Characteristics of intervention**

Mother and infant pairs with attachment problems (e.g. infant slipping off the breast) were given small, ultra-thin nipple shields by advanced nurse practitioners who continued to support the mothers. The feed immediately before the nipple shield was first introduced was used as the comparison for the first feed with the shield, hence mothers acted as their own controls. Mothers used the shields for a mean of 32.5 days. No information is reported about transfer from use of the shield to feeding without it.

There is no indication of any non-compliance and no indication of any exclusions.

**Outcome assessment**

The primary outcome was milk transfer, measured by test weighing of the infant before and after feeds. Duration of breastfeeding for the whole group (all of whom went on to use the shields) was measured. No longer-term milk transfer, clinical/health outcomes, process, psychosocial or cost outcomes are reported.

**Methodological quality of included study**

The quality of this crossover study was rated as ‘moderate’ (Table 78 in Appendix 5).

**Effectiveness of intervention****Primary outcomes**

The results<sup>136</sup> indicate an increase in milk transfer with the use of the shield. Mean milk transfer (SD) with the shield was increased by 14.4 (9.1) ml,  $t = 9.25$ ,  $p = 0.0001$ , paired Student’s  $t$ -test. The range was 2–41 ml and the SD is large, indicating a varied response to its use. It is reported that all infants consumed more milk in the feed with the shield than without. No information on breastfeeding outcomes is available.

**Secondary outcomes**

No secondary outcomes are reported.

**Expressing breastmilk interventions**

A total of six primary studies<sup>112,114,125,128,134,142</sup> evaluating methods of expressing breastmilk were identified. As detailed in Table 5, four of the six were included in one systematic review. Four of the six studies were conducted in industrialised country settings, including two in the UK.

**Results from randomised controlled trials and randomised crossover studies**

Five RCTs<sup>112,114,125,128,142</sup> and one randomised crossover study<sup>134</sup> of methods of expressing breastmilk interventions were identified (see Tables 44–49 in Appendix 4.1).

Two of the six studies<sup>115,125</sup> are linked with studies of additional interventions to enhance breastmilk production that appear in the next section of this review (see Additional interventions to enhance breastmilk production). Data from Fewtrell *et al.* (2001)<sup>125</sup> are used in a later oxytocin trial<sup>144</sup> for comparison purposes, and Jones *et al.* (2001)<sup>115</sup> report both a breast pumping RCT and a randomised crossover trial of breast massage prior to pumping.

**Characteristics of participants**

Four of the six included trials were performed in industrialised country settings, two in the UK<sup>115,125</sup> and two in the USA.<sup>112,128</sup> The remaining two trials took place in India<sup>134</sup> and Kenya and Nigeria.<sup>142</sup>

All trials recruited mothers providing expressed breastmilk for their infants hospitalised in neonatal units. None aimed to recruit mothers of a particular age, socioeconomic status or parity.

**TABLE 5** Included studies for 'Expressing breastmilk interventions'

Primary paper	Study design (n analysed) <sup>a</sup>	Inclusion in existing systematic review	Country
Fewtrell 2001 <sup>125</sup>	RCT (n = 167) (infants)	McInnes 2006 <sup>161</sup>	UK
Groh-Wargo 1995 <sup>128</sup>	RCT (n = 32)	McInnes 2006 <sup>161</sup>	USA
<sup>b</sup> Hill 1999b <sup>112</sup>	RCT (n = 39)	No	USA
Jones 2001 <sup>114</sup>	RCT (n = 36)	McInnes 2006 <sup>161</sup>	UK
Paul 1996 <sup>134</sup>	Randomised crossover trial (two phases: n = 22, n = 14)	McInnes 2006 <sup>161</sup>	India
Slusher 2007 <sup>142</sup>	RCT (n = 65)	No	Kenya and Nigeria

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

b Three papers, Hill 1999a,<sup>111</sup> Hill 1999b<sup>112</sup> and Hill 2001,<sup>113</sup> report the same study.

The mothers included in three of the trials had a mean age in the late twenties<sup>112,125,128</sup> and in a fourth trial the mothers from Kenya and Nigeria had a mean age in the mid-twenties. Age of the mothers was not reported for the other two trials.<sup>115,134</sup> On the basis of education, income, marital status and race details reported, the participants in the US studies<sup>112,128</sup> and one of the UK studies<sup>125</sup> were of mixed and not predominantly high or low socioeconomic status; these details are not reported for the other three studies. Around 60% of participants in three studies were multiparous,<sup>114,125,142</sup> with smaller proportions of multiparous mothers in the two US studies<sup>112,128</sup> and parity not reported in one study.<sup>134</sup> Previous preterm births were not reported in any of the six studies.

In the four studies from industrialised countries,<sup>112,114,125,128</sup> 20–40% of participants had previous breastfeeding experience, with 15% of participants in one of these studies<sup>125</sup> having previous experience of expressing breastmilk. The studies from India<sup>134</sup> and Kenya and Nigeria<sup>142</sup> did not report breastfeeding or pumping experience. The percentage of mothers who had had multiple births ranged from 14% to 23% in three studies<sup>112,114,125</sup>; multiple births were not reported for the other three studies. With regard to providing breastmilk for their infants, participants in the two US studies had to be either expecting to provide breastmilk exclusively by mechanical expression (electric pump) for at least 6 weeks,<sup>112</sup> or to have pumped for 4 weeks.<sup>128</sup> Mothers in the two UK studies had to have decided to provide milk for their infant<sup>125</sup> or to be expressing at least

five times a day before study entry.<sup>114</sup> The studies from India<sup>134</sup> and Kenya and Nigeria<sup>142</sup> specified only that participants had to be mothers of infants unable to breastfeed.

In all six studies, recruitment took place during the infant's first week of life. The two US trials recruited only mothers of very low birthweight (VLBW) infants ( $\leq 1500$  g).<sup>112,128</sup> The infants of mothers included in one UK study<sup>125</sup> had a mean (SD) birthweight of 1357 (540) g in the intervention group and 1305 (565) g in the control group; in the other UK study<sup>114</sup> mean birthweight was 1535 g (SD not reported). Mean gestational age of infants included in three of the four studies carried out in industrialised country settings was 28–30 weeks;<sup>112,114,125</sup> gestational age was not reported for the fourth of these studies.<sup>128</sup> Birthweight and gestational age of infants in the studies from India and Kenya and Nigeria differed from those in the US and UK studies. The study from India<sup>134</sup> included infants whose mean gestational age was 34 weeks (range 27–40 weeks, birthweight not reported) and the study from Kenya and Nigeria<sup>142</sup> included infants with mean gestational age of 32 weeks (range 26–40 weeks) whose mean birthweight was 1709 g (range 907–4600 g). Three study reports state that no infant was breastfeeding.<sup>112,134,142</sup> One study report states that mothers left the study when their infant was 'breastfeeding freely'; attempts to breastfeed before this point are not mentioned.<sup>128</sup> In one study, 70% of mothers attempted to breastfeed;<sup>125</sup> results are reported separately for this subgroup of participants. One study report does not state whether or not infants were breastfeeding.<sup>114</sup>

### Characteristics of interventions

Interventions to assist mothers with breastmilk expression include both techniques/equipment and regimens for expressing breastmilk.

### Techniques/equipment for expressing breastmilk

Hand expression was evaluated in the studies from India<sup>134</sup> and Kenya and Nigeria,<sup>142</sup> but techniques of hand expression were not described.

Hand-operated pumps were evaluated in two studies<sup>125,134</sup> and a foot-operated pump in one study.<sup>142</sup> One of these studies acknowledges funding from the manufacturer;<sup>125</sup> in the other two, funding sources are not reported. The hand-operated pump in the study by Fewtrell *et al.*<sup>125</sup> (Philips Avent ISIS, Philips, UK) was newly designed with petal cushions to simulate the infant's compressive action on the areola during breastfeeding rather than simply operating by suction. The hand-operated pump in the study by Paul *et al.*<sup>134</sup> in India was a Medela cylindrical pump made of plastic material, with a piston mechanism which, by in-and-out motion with one hand, produced suction at the breast cup as applied around the areola; the vacuum-sucked breastmilk then flowed into a receptacle-cum-bottle. A recent systematic review<sup>161</sup> states this type of pump is not currently in use in the UK. The study in Kenya and Nigeria by Slusher *et al.*<sup>142</sup> tested a double collection non-electric pedal pump.

Five of the six studies<sup>112,114,125,128,142</sup> evaluated electrically powered pumps. One of these studies acknowledges partial funding from the pump manufacturer;<sup>128</sup> four acknowledge funding from other sources (research grant;<sup>128</sup> university;<sup>112</sup> a charity;<sup>114</sup> the hand-pump manufacturer<sup>125</sup>) and funding sources are not reported for one study.<sup>142</sup> The two UK studies<sup>114,125</sup> both used Egnell Ameda pumps (Egnell Ameda, Taunton, Somerset, UK). Fewtrell *et al.*<sup>125</sup> described the Egnell Ameda pump in their study as large, operating by suction, regarded as the gold standard and used in 94% of UK neonatal units. Jones *et al.*<sup>114</sup> state that the Egnell Ameda Electric Elite™ pump was used in their study because it created periodic and limited phases of negative pressure, and converted easily to simultaneous pumping mode. Jones *et al.*<sup>114</sup> selectively provided silastic shield inserts so that shield size and breast size could be matched. The two US studies and the study performed in Kenya and Nigeria used Medela pumps (Medela, Inc., McHenry, IL, USA). The pumps in the study by Groh-Wargo *et al.* (1995)<sup>128</sup> are described as the

Medela single electric pump and the Medela bilateral electric breast pump; those in Hill *et al.*<sup>112</sup> as Medela Lactina™; and that in Slusher *et al.*<sup>142</sup> as a double-collection Lactina electric breast pump.

The techniques and equipment used for expressing breastmilk in the six studies, and the mode of operation of the equipment, are summarised in Table 6.

### Regimens for expressing breastmilk

Three of the six studies specifically compared single/unilateral/sequential pumping with double/bilateral/simultaneous pumping<sup>112,114,128</sup> and this was a factor in another two of the studies.<sup>125,142</sup> Double pumping was not possible in the sixth study.<sup>134</sup> Comparisons for the six studies were as follows:

- novel manual breast pump (Avent ISIS) (single mode only) versus standard electric breast pump (Egnell Ameda) in single or double mode according to the mother's preference<sup>125</sup>
- Egnell Ameda Electric Elite (with silastic shield inserts as appropriate) in sequential (single) mode versus the same pump in simultaneous (double) mode<sup>114</sup> (this study also tested massage versus no massage before both modes of pumping in a crossover design – see Additional interventions to enhance breastmilk production)
- Medela double pump versus Medela single pump<sup>128</sup>
- Medela Lactina double pump versus Medela Lactina single pump<sup>112</sup>
- double-collection Lactina electric breast pump versus double-collection non-electric pedal pump versus hand expression<sup>142</sup>
- hand-operated Medela cylindrical pump versus hand expression.<sup>134</sup>

Protocols of all six trials prescribed how often mothers should express breastmilk. In descending order of frequency these were as follows: 2–3 hourly;<sup>142</sup> eight sessions per day;<sup>112,114</sup> six or more sessions per day;<sup>125</sup> 3-hourly except at night, with four or more sessions per day;<sup>128</sup> and three per day at 10.00, 12.00 and 14.00.<sup>134</sup> In the study by Paul *et al.*<sup>134</sup> the three daily sessions were the ones at which study data were collected and it is not clear whether these were or were not the only expression sessions.

Protocols of all six trials prescribed the duration of the milk expression sessions. Two wanted mothers to express for given durations; 15 minutes<sup>134</sup> and initially 5 minutes per breast then increasing

**TABLE 6** Techniques and equipment for expressing breastmilk and their modes of operation

Study	What was used to express breastmilk? <sup>a</sup>	How did this technique/equipment work?
Paul 1996 <sup>134</sup>	Hand expression	Not described
	Hand-operated pump (Medela cylindrical)	Suction, vacuum
Slusher 2007 <sup>142</sup>	Hand expression	Not described
	Foot-operated pump (double-collection, non-electric)	Not described
	Electric pump (Double-collection Lactina)	Suction <sup>b</sup>
Fewtrell 2001 <sup>125</sup>	Hand-operated pump (ISIS)	Not simply by suction: had 'petals' to simulate the infant's compressive action on the areola
	Electric pump (Egnell Ameda)	Suction
Jones 2001 <sup>114</sup>	Electric pump (Egnell Ameda)	Suction, negative pressure
Groh-Wargo 1995 <sup>128</sup>	Electric pump (Medela single, Medela bilateral)	Suction <sup>b</sup>
Hill 1999b <sup>112</sup>	Electric pump (Medela Lactina)	Suction <sup>b</sup>

a Names of pumps are as reported in the papers.  
b www.medela.co.uk/UK/breastfeeding/products/lactina.php, accessed 28 October 2008.  
c Jones 2001 reports findings from an expressing breastmilk intervention (RCT) and an additional intervention to enhance milk production (randomised crossover study) and appears in each of those sections.

time per breast.<sup>125</sup> Two trials wanted mothers to express until milk flow ceased: 'until milk droplets cease flowing'<sup>142</sup> or 'until milk no longer appears in collection set'.<sup>115</sup> One trial combined these approaches,<sup>112</sup> asking mothers to express for 'a minimum of ten minutes per breast or until breast no longer dripping' and one protocol changed during the study from 20 minutes to 'as long as there is any flow of milk'.<sup>128</sup> None of the six trials prescribed an amount of milk to be expressed.

Studies varied in how long expression continued. Three studies were completed during the second week after the birth; two of these<sup>114,134</sup> took place over two 48-hour periods and were completed by postnatal day 11, and in the third<sup>142</sup> all mothers had completed the study by postnatal day 13. In contrast, the mothers in the study by Fewtrell *et al.* (2001)<sup>125</sup> participated for a median of 15 days with a wide range; the criteria for ending study participation were if and when the mother stopped using the assigned pump, stopped filling in data forms, or the infant was fully breastfed, transferred, discharged or died. Mothers in the the two US studies<sup>112,128</sup> contributed data for at least 4 weeks, until 4–7 weeks after giving birth.

### Standard care

Details of care of the mothers and infants other than those of the milk expression interventions were lacking in these study reports. One states that

the study unit had an active breastfeeding policy,<sup>114</sup> another reports that kangaroo care took place on the unit.<sup>112</sup>

### Outcome assessment

#### Primary outcomes

##### Breastfeeding/breastmilk-related outcomes

All six trials reported breastmilk production, by volume<sup>125,128,134,142</sup> or weight.<sup>112,114</sup> Two trials reported breastmilk feeding/breastfeeding, either at discharge<sup>125</sup> or at term.<sup>114</sup> No other primary outcomes for this review were reported by intervention group, although some were presented in subgroup analyses.<sup>112,125</sup>

#### Secondary outcomes

##### Clinical/health outcomes

Two of the six trials reported clinical/health outcomes. Fewtrell *et al.* (2001)<sup>125</sup> reported clinical outcomes both for infants (NEC, oxygen supplementation and ventilation) and for mothers (sore nipples, engorgement, mastitis and use of metoclopramide) and Groh-Wargo *et al.* (1995)<sup>128</sup> reported serum prolactin. The other four trials did not report clinical/health outcomes.<sup>112,114,134,142</sup>

##### Process outcomes

Three of the six trials reported pumping frequency<sup>112,125,128</sup> and two of the three<sup>125,128</sup> also reported the time that mothers spent pumping. Jones *et al.* (2001)<sup>114</sup> mention time spent pumping.

The other two trials<sup>134,142</sup> did not report process outcomes.

### Psychosocial outcomes

Mothers' views of the methods of milk expression used in trials were reported for three studies.<sup>114,125,134</sup> Psychosocial outcomes were not reported for the other three studies.<sup>112,128,142</sup>

### Cost-effectiveness outcomes

None of the six trials reported cost-effectiveness outcomes.

### Methodological quality of included trials

One trial was rated as 'good' quality overall.<sup>125</sup> Three trials were rated as 'moderate' quality.<sup>114,128,142</sup>

The remaining two trials were considered to be 'poor' quality.<sup>112,134</sup> Serious caution is warranted in interpretation of the results of these trials. Details of the quality ratings for each trial are provided in Table 79 in Appendix 5.

### Effectiveness of interventions

#### Primary outcomes

For maternal outcomes of four studies<sup>112,114,125,142</sup> estimations of effectiveness could not be calculated on an ITT/postrandomisation exclusions basis.

All six trials reported breastmilk production, by volume<sup>125,128,134,142</sup> or weight.<sup>112,114</sup> The breastmilk production primary outcome was reported for all six studies using continuous data. To present individual estimated relative risks in forest plots we therefore needed to extract the number in each treatment group with the mean and standard deviation of the outcome. These numbers were reported for only one of the six studies;<sup>128</sup> the other five did not report standard deviations. Breastmilk feeding was reported for two studies<sup>114,125</sup> using categorical data. It was possible to work out

relevant numbers from one study report<sup>125</sup> but not from the other.<sup>114</sup>

### Breastmilk production

These results do not show any statistically significant difference in the weekly breastmilk volumes expressed by 16 mothers randomised to simultaneous (double) pumping (Medela) compared with 16 mothers randomised to sequential (single) pumping (Medela)<sup>128</sup> (Figure 16).

Two of the five remaining studies<sup>112,125</sup> reported no significant differences between the groups for their breastmilk production outcomes. The other three<sup>115,134,142</sup> reported significant differences in their breastmilk production outcomes. In Jones *et al.* (2001)<sup>115</sup> (no time restrictions on pumping) weight of milk from a single expression (g) (95% CI) was 51 (46–56) without massage and 79 (73–85) with massage in the sequential pumping group versus 88 (79–97) without massage and 125 (110–140) with massage in the simultaneous pumping group ( $p < 0.01$ ). Paul *et al.* (1996)<sup>134</sup> reported a greater mean output per session (ml) (SD) in the hand-powered pump group than in the hand expression group both on days 4 and 5 [46.8 (26.3) versus 31.2 (15.5);  $t = 3.29$  (Student's  $t$ -test);  $p < 0.01$ ] and on days 8 and 9 [50.4 (13.4) versus 38.4 (11.2);  $t = 4.42$  (Student's  $t$ -test);  $p < 0.01$ ]. Slusher *et al.* (2007)<sup>142</sup> reported mean (range) breastmilk volumes (ml/day) of 578 (135–1051) in the electric double-pump group versus 463 (85–1315) in the double-collection pedal pump group versus 323 (93–812) in the hand expression group (significantly different only between the electric double-pump group and the hand expression group,  $p < 0.01$ ).

### Breastmilk feeding

The numbers reported here (Figures 17 to 20) are based on all the infants of randomised

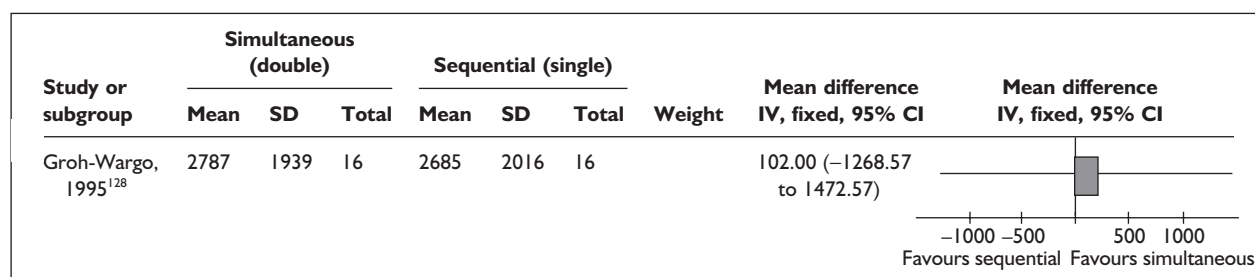


FIGURE 16 Double vs single electric pumping: breastmilk production (ml/week, up to 6 weeks after the birth).

mothers. The unit of allocation in this study<sup>125</sup> was mothers, and the paper did not report any postrandomisation exclusions of infants. The study authors make the point that twins and triplets would be expected to reduce the proportion of infants receiving breastmilk, and to some extent this is shown above. However, none of these results show any statistically significant differences in breastmilk intake at discharge or transfer between the infants of mothers randomised to the Avent ISIS hand-powered pump and the infants

of mothers randomised to the Egnell Ameda electrically powered pump (single or double pumping according to mothers' preference), whether all infants or only singleton infants are included in the analysis.

### Secondary outcomes

#### Clinical/health outcomes

Fewtrell *et al.*<sup>125</sup> found no significant differences between the groups for infants with NEC, oxygen supplementation or ventilation, and similar

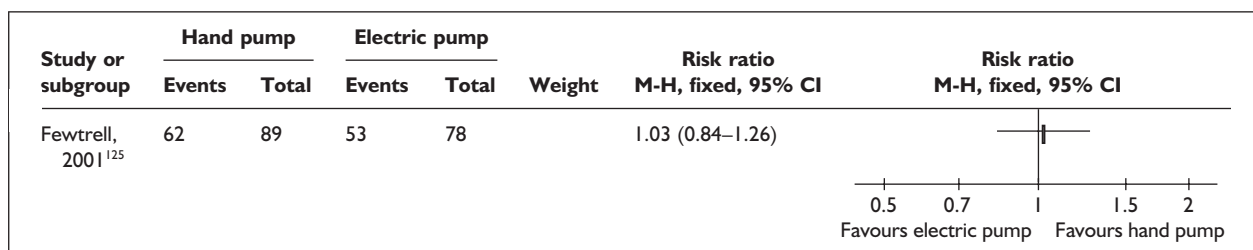


FIGURE 17 Hand pump vs electric pump: any breastmilk feedings at discharge or transfer (all infants).

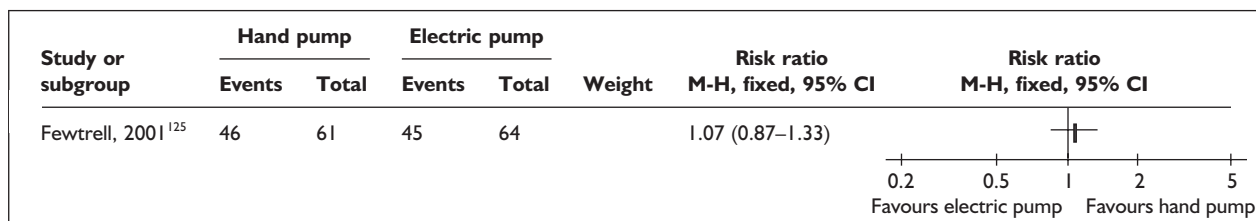


FIGURE 18 Hand pump vs electric pump: any breastmilk feedings at discharge or transfer (singletons).

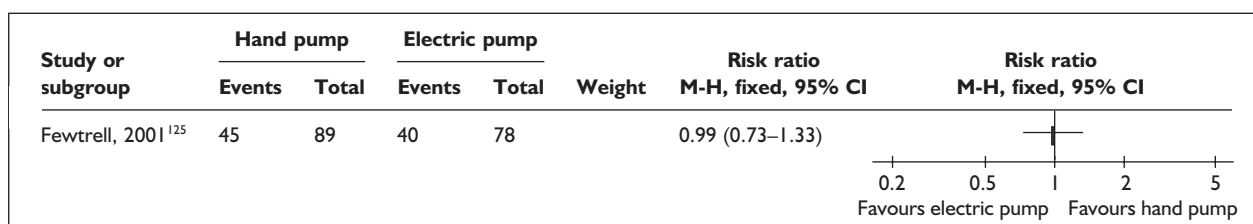


FIGURE 19 Hand pump vs electric pump: > 50% intake as breastmilk at discharge or transfer (all infants).

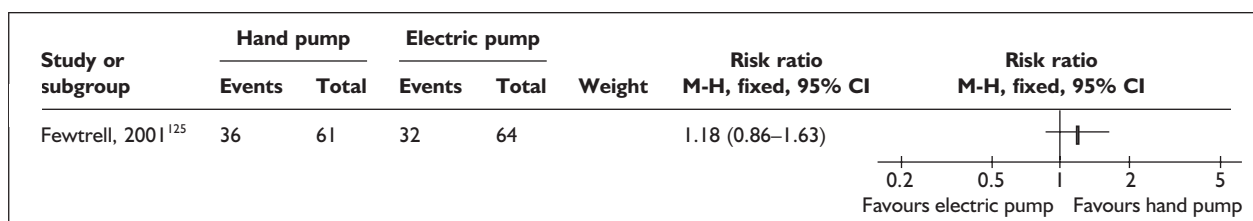


FIGURE 20 Hand pump vs electric pump > 50% intake as breastmilk at discharge or transfer (singletons).

proportions of mothers from each group with sore nipples, engorgement and use of metoclopramide. Two mothers in the electric pump group developed mastitis. Fewtrell *et al.*<sup>125</sup> reported other psychosocial measurements during two days in the second postnatal week from a subsample of 45 mothers (31%). Groh-Wargo *et al.*<sup>128</sup> found no difference between groups in serum prolactin. Clinical/health outcomes were not reported for four studies.<sup>112,114,134,142</sup>

### **Process outcomes**

Process outcomes were not reported in two of the six included trials.<sup>134,142</sup> Three trials reported that pumping took place less frequently than specified in study protocols.<sup>112,125,128</sup> Two of the three reported the time mothers spent pumping. Fewtrell *et al.*<sup>125</sup> found mothers randomised to the electric pump spent significantly less time per day expressing (median 51 minutes, 25th/75th centiles 38, 63) than mothers randomised to the manual pump (median 65 minutes, 25th/75th centiles 56, 85;  $p < 0.001$ ). Electric pump users could express either simultaneously or sequentially, whereas manual pump users could only express sequentially. In a subgroup of 45 mothers (31%), however, Fewtrell *et al.*<sup>125</sup> found that mothers who used the manual pump took significantly less time to express a given volume of milk than mothers who were using the electric pump. In this subgroup Fewtrell *et al.*<sup>125</sup> also found that mothers who attempted to breastfeed had significantly higher total number of expressions and total volume expressed than mothers who did not attempt to breastfeed (both  $p < 0.001$ ). Groh-Wargo *et al.*<sup>128</sup> found that 16 mothers allocated to sequential pumping spent a mean (SD) 11.1 (3.1) hours per week pumping, compared with 7.6 (3.0) hours per week for 16 mothers allocated to simultaneous pumping ( $p = 0.003$ ). In addition, Jones *et al.*<sup>114</sup> report that mothers allocated to simultaneous pumping took about 10–15 minutes per session compared with 25–40 minutes for women allocated to sequential pumping.

### **Psychosocial outcomes**

Mothers' views of the methods of milk expression used were reported for three studies. Fewtrell *et al.*<sup>125</sup> reported that mothers gave the manual pump better ratings overall and for 'comfort' and 'pleasant to use' than the electric pump. Mothers in the study of Jones *et al.*<sup>114</sup> appreciated the time saved by simultaneous pumping and pointed out the need for pumps to have larger collection sets. Paul *et al.*<sup>134</sup> found that on days 4–5 mothers preferred the cylindrical pump because it provided

relief from engorgement; however, on days 8–9 they preferred hand expression because it was more gentle and convenient. Psychosocial outcomes were not reported for the other three studies.<sup>112,128,142</sup>

### **Cost-effectiveness outcomes**

Fewtrell *et al.*<sup>125</sup> reported that the hand-powered pump in their study cost 'tens of pounds' compared with 'hundreds of pounds' for the same study's large electric pump. None of the six trials reported cost-effectiveness outcomes.

## **Results from other study designs**

No studies of methods of expressing breastmilk using designs other than randomised trials were identified.

## **Additional interventions to enhance breastmilk production**

A total of seven primary studies and two systematic reviews evaluating additional interventions to enhance milk production were identified. As detailed in *Table 7*, three primary studies were included in at least one of the two systematic reviews. All seven studies were conducted in industrialised country settings including two in the UK.<sup>114,144</sup>

## **Results from RCTs and randomised crossover studies**

Seven studies of additional interventions to enhance milk production were identified; five were RCTs<sup>116,123,133,144,146</sup> and two were randomised crossover studies<sup>114,148</sup> (*Tables 50–56* in Appendix 4.1).

Two of the seven studies<sup>114,144</sup> are linked with studies of expressing milk interventions that appear in the previous section (see *Expressing breastmilk interventions*). Fewtrell *et al.* (2006)<sup>144</sup> use data from the earlier breast pump study<sup>125</sup> for comparison purposes, and Jones *et al.*<sup>114</sup> report both a breast pumping RCT and a randomised crossover study of breast massage prior to pumping.

### **Characteristics of participants**

All seven studies were conducted in industrialised country settings including two in the UK,<sup>114,144</sup> three in the USA,<sup>116,146,148</sup> one in Canada<sup>123</sup> and one in New Zealand.<sup>132</sup>



**TABLE 7** Included studies for 'additional interventions to enhance milk production'

Primary paper	Study design (n analysed) <sup>a</sup>	Inclusion in existing systematic review	Country
da Silva 2001 <sup>123</sup>	RCT (n = 16)	Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	Canada
Feher 1989 <sup>146</sup>	RCT (n = 55)	No	USA
Fewtrell 2006 <sup>144</sup>	RCT (n = 51)	No	UK
Gunn 1996 <sup>133</sup>	RCT (n = 18)	McInnes 2006 <sup>161</sup>	New Zealand
Hansen 2005 <sup>116</sup>	RCT (n = 57)	Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	USA
<sup>b</sup> Jones 2001 <sup>114</sup>	Randomised crossover study (n = 36)	No	UK
Mersmann 1993 <sup>148</sup>	Randomised crossover study (n = 18)	No	USA

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

b Jones 2001 reports findings from an expressing breastmilk intervention (RCT) and an additional intervention to enhance milk production (randomised crossover study) and appears in each of those sections.

All the studies included mothers who had given birth to preterm infants being cared for in neonatal units. None aimed to recruit mothers of a particular age, socioeconomic status or parity. The mothers included in three studies had a mean or median age in the twenties;<sup>116,123,146</sup> in three studies the mean age of the mothers was in the thirties;<sup>132,144,148</sup> and in one study age of the mothers was not reported.<sup>114</sup> Participants in three studies appeared to be of above average socioeconomic status,<sup>116,144,148</sup> with fewer of these details reported by an older study from the USA<sup>146</sup> and none in three study reports.<sup>114,123,133</sup> In one study<sup>133</sup> 3/18 participants (17%) were multiparous; the other six studies included higher proportions of multiparous mothers,<sup>114,116,123,144,146,148</sup> with one of these<sup>116</sup> reporting 21/60 participants (35%) having had a previous preterm birth. Forty-two percent of the mothers in one study (Jones *et al.*, 2001),<sup>114</sup> 33% in another<sup>148</sup> and 20% in a further two studies<sup>123,144</sup> had previous breastfeeding experience. Two studies<sup>144,148</sup> reported that around 18% of mothers had previous pumping experience. Only mothers who were expressing at least five times per day were enrolled into the study of Jones *et al.*;<sup>114</sup> none of the other studies report a minimum expression inclusion criterion. In five studies, around 18% of mothers had just had multiple births;<sup>114,116,123,144,148</sup> the other two studies did not report multiple births.

Four of the seven studies reported birthweight. Mean birthweight was < 1500 g (VLBW) in two studies<sup>133,144</sup> (standard deviations indicate wide ranges); in one study<sup>114</sup> mean birthweight was 1535 g (standard deviation not reported) and in another,<sup>148</sup> median birthweight was 1533 g and all but 2/21 infants were VLBW ( $n = 10$ ) or LBW ( $n = 9$ ). Three studies did not report birthweight.<sup>116,123,146</sup> Mean or median gestational age in six of the seven studies was between 28 and 30 weeks; in the seventh<sup>148</sup> median gestational age was 32 weeks. In two studies<sup>116,144</sup> randomisation was stratified by gestational age, and one study<sup>148</sup> grouped infant gestational ages (< 30 weeks, 30–34 weeks and > 34 weeks). Two other studies reported mean gestational age with standard deviations,<sup>123,133</sup> and in two study reports<sup>114,146</sup> there was no indication of the range of gestational age of the infants.

Infant feeding at the breast is an important participant factor related to enhancing milk production. Two of the seven studies report that no infant was breastfeeding<sup>123,148</sup> and two<sup>116,133</sup> report that some infants were breastfeeding. One of these<sup>133</sup> included older infants and calculated the amount of milk taken by weighing the infant before and after breastfeeds. The other<sup>116</sup> included only recently born preterm infants and no measures of milk intake are reported. The three studies that

did not report breastfeeding all reported short-term interventions with recently born preterm infants.<sup>114,144,146</sup>

### **Characteristics of interventions**

Of the seven studies, four RCTs<sup>116,123,133,144</sup> investigated galactagogues. One RCT<sup>146</sup> and two randomised crossover studies<sup>114,148</sup> investigated other interventions to enhance milk production; a relaxation/imagery tape;<sup>146</sup> breast massage prior to expression<sup>114</sup> and therapeutic touch (TT).<sup>148</sup>

### **Galactagogues**

Four different galactagogues were each evaluated in one double-blind, placebo-controlled RCT. Two of these<sup>116,144</sup> recruited mothers who had recently given birth to their preterm infants. The intervention in the study by Fewtrell *et al.*<sup>144</sup> was a five-day course of oxytocin nasal spray. Participants in this study also received extra support from the research nurse, who saw each mother daily and was available by telephone. This study was funded by a Medical Research Council (MRC) programme grant. The intervention in the study by Hansen *et al.*<sup>116</sup> was a 10-day course of oral metoclopramide 10 mg three times per day. This study was jointly supported by grants from the National Institutes of Health and Children's Miracle Network. The other two galactagogue studies<sup>123,133</sup> recruited mothers who had been expressing for varying lengths of time (mean length of time after the birth that the intervention started was over a month in both studies) and whose milk production was not meeting their infant's needs. The intervention in the study by da Silva *et al.*<sup>123</sup> was a 7-day course of oral domperidone 10 mg three times per day, and the intervention adopted by Gunn *et al.*<sup>133</sup> was a 7-day course of recombinant human growth hormone (hGH) 0.2 IU/kg/day subcutaneously to a maximum of 16 IU/day. This latter study was jointly supported by the Health Research Council of New Zealand and Pharmacia AB, Stockholm, Sweden; the study by da Silva *et al.*<sup>123</sup> was funded by a grant from the Research and Education Foundation of the Canadian Society of Hospital Pharmacists.

### **Other interventions to enhance milk supply**

A 20-minute audio cassette of relaxation/imagery techniques was evaluated in a RCT.<sup>146</sup> The tape consisted of a progressive relaxation exercise followed by a guided imagery section. Mothers were recommended to use the tape every time they wanted to express milk. This study was partially funded by a grant from the National Institutes of Health.

Two related interventions, a RCT of simultaneous versus sequential pumping (see Expressing breastmilk interventions) and a randomised crossover study of breast massage versus no breast massage prior to pumping, were reported in one paper.<sup>114</sup> Breast massage was carried out by the mother and consisted of gentle tactile stimulation of mammary and nipple tissue using a hand action that rolled the knuckles downwards over the breast, beginning at the ribs and working towards the areola. Breast massage did not involve manual expression of milk. This study by Jones *et al.*<sup>114</sup> took place over four days and all mothers included in the analyses had begun by day 7. The latter study was funded by Baby Lifeline.

Mersmann<sup>148</sup> based her randomised crossover study on an association between relaxation and letdown, and literature on Therapeutic Touch (TT) that suggests TT decreases anxiety and impacts other physiological manifestations of relaxation. The TT group received therapeutic touch, which consisted of hand movements 2–4 inches above the whole of the mother's body, with certain therapeutic awareness and intentionality on the part of the nurse. In the mimic therapeutic touch (MTT) group, hand movements were indistinguishable from those of TT, but MTT nurses counted instead of exercising the awareness and intentionality required in TT. A control group had neither treatment (NT). Mothers were required to have been expressing for at least 2 weeks, and at study entry half (9/18) of the included mothers had been expressing for 14–20 days, two (11%) for 21–27 days, three (17%) for 4–5 weeks and four (22%) for 6 weeks or more.<sup>148</sup> Funding for this study is not reported.

### **Standard care**

Four of the seven studies were undertaken with mothers of recently born preterm infants, and in three of these,<sup>114,116,146</sup> all the mothers appear at least to have received verbal and written instructions on how to use the electric breast pump, and had access to a pump. In addition, the UK unit in which one study<sup>114</sup> was undertaken had an active breastfeeding policy and mothers had opportunity to view a video made by the researchers covering milk expression and preterm breastfeeding. In the fourth study with mothers of recently born preterm infants,<sup>144</sup> undertaken in another UK unit, mothers were advised to express milk at least every 3 hours and instructed in the use of hand massage before pumping, with advice being provided by neonatal unit and postnatal ward staff.

In one study unit in the USA,<sup>148</sup> the mothers had access to breastfeeding pamphlets and an electric breast pump that were stored in a newly built breastfeeding cubicle. This had an opaque, approximately 1.8 metre glass wall, offering mothers some degree of privacy for expression and breastfeeding. However, at the time of the study mothers of preterm infants who were not breastfeeding were neither encouraged to express nor discouraged from expressing milk; infants did not initiate breastfeeding until they were successful at bottle feeding; lactation educators were available on request but generally assisted with breastfeeding; and kangaroo care was not practised. In the study unit in Canada where da Silva *et al.*<sup>123</sup> performed the domperidone study, extensive teaching by lactation consultants for all women failing lactation was provided and only mothers continuing to have problems after this teaching were recruited to the study. Management before the point of lactation failure was not reported. Gunn *et al.*<sup>133</sup> did not describe standard care but stated that in the New Zealand unit where the hGH study was performed there was a well-established support system provided by hospital staff, and 90% of mothers were discharged breastfeeding, similar to the wider New Zealand data for preterm and term infants.

### Outcome assessment

#### Primary outcomes

All seven studies reported the amount of milk expressed, either by volume<sup>116,123,133,146,148</sup> or, in the two UK studies,<sup>114,144</sup> by weight. Statistical challenges of reporting amounts of milk are discussed in two of the papers<sup>144,148</sup> and addressed differently in different studies. Fat content of milk expressed was reported for the whole study sample by three studies<sup>114,146,148</sup> and for a subgroup of participants by Fewtrell *et al.*<sup>144</sup> Breastfeeding at term (37 weeks) was reported by Jones *et al.*,<sup>114</sup> and Hansen *et al.*<sup>116</sup> reported median duration of breastfeeding.

#### Secondary outcomes

The four galactagogue studies<sup>116,123,133,144</sup> discussed safety, and three reported drug/hormone levels.<sup>116,123,133</sup> In addition, one of these studies reported reasons mothers gave for stopping expressing.<sup>116</sup> Four studies reported rates of breastmilk expression<sup>114,133,144,148</sup> and four reported mothers' views.<sup>114,144,146,148</sup> None of the studies reported cost-effectiveness outcomes.

#### Methodological quality of included trials

One RCT was rated as 'good' quality overall.<sup>144</sup> Four RCTs<sup>116,123,133,146</sup> and two randomised crossover

studies<sup>114,148</sup> were rated as 'moderate' quality (see *Table 80* in Appendix 5).

### Effectiveness of interventions

#### Primary outcomes

One double-blind, placebo-controlled RCT of oxytocin spray for mothers of recently born preterm infants<sup>144</sup> found no significant difference between the groups in total milk weight over days 1–5. Milk production was significantly higher in the intervention group on day 2 only; results then converged. Individual plots presented for each mother on each day show the variability between mothers in both groups. In a subgroup analysis of fat content of milk expressed, no significant differences between the groups were found.

One double-blind, placebo-controlled RCT of metoclopramide for mothers of recently born preterm infants<sup>116</sup> found no significant difference between the groups on any study day.

One double-blind, placebo-controlled RCT of domperidone that included mothers of older preterm infants<sup>123</sup> compared the difference between mean milk volume at baseline and mean milk volume over study days 2–7 for seven mothers in the intervention group and nine in the placebo group. Mean volume increased significantly more in the intervention group. The sample was small and the standard deviations and confidence interval wide, as illustrated in the forest plot shown in *Figure 21*.

One double-blind, placebo-controlled RCT of human growth hormone (hGH) that included mothers of older preterm infants<sup>133</sup> compared mean daily milk volume over study days 0–1 with mean milk volume on day 8 for nine mothers in each group. Mean milk production (SD) over 2 days at baseline was 139 (49) ml/day in the intervention group compared with 93 (50) ml/day in the control group. On study day 8 after the 7 days' treatment, mean milk production increased to 175 (46) ml/day in the hGH group ( $p < 0.01$ ) compared with 102 (69) ml/day (NS).

One RCT of a relaxation/imagery tape for mothers of recently born preterm infants<sup>146</sup> compared mean milk volume at a single expression during the second postnatal week between 30 mothers in the intervention group and 25 mothers in the control group. Mean milk volume was significantly greater in the intervention group. The confidence interval and standard deviations were wide, as illustrated in the forest plot shown in *Figure 22*.

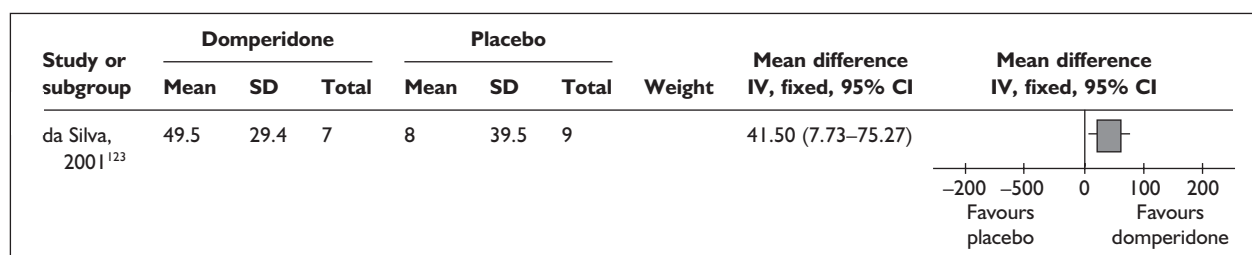


FIGURE 21 Domperidone vs placebo: change in mean milk volume.

The fat content of a sample was analysed using a creamatocrit test. No statistically significant difference was found between the groups, as illustrated in the forest plot shown in Figure 23.

One randomised crossover study of breast massage prior to milk expression for mothers of recently born preterm infants<sup>114</sup> randomised mothers to perform breast massage before pumping on either days 1 and 2 or days 3 and 4 of the study, and not to perform massage on the other pair of days. These mothers were taking part concurrently in a linked RCT of simultaneous versus sequential pumping (see Expressing breastmilk interventions). Complete data from 36 mothers on day 2 and day 4 were analysed and results of the two interventions are presented together as milk yield per expression in Table 8.

The authors concluded that simultaneous pumping was more effective at producing milk than sequential pumping ( $p < 0.01$ ) and that breast massage had an additive effect, improving milk production in both groups. It was reported that fat concentration in the milk was not affected by the increase in volume achieved by the interventions.

In a randomised crossover study<sup>148</sup> of therapeutic touch (TT) that included mothers of older preterm infants, the author reported that five mothers experienced leaking of breastmilk during TT compared with one mother during mock TT ( $p < 0.05$ ). The mean (SD), median and range of volumes of milk expressed after study treatments (not adjusted for milk leaked) by the 18 mothers are reported in Table 9.

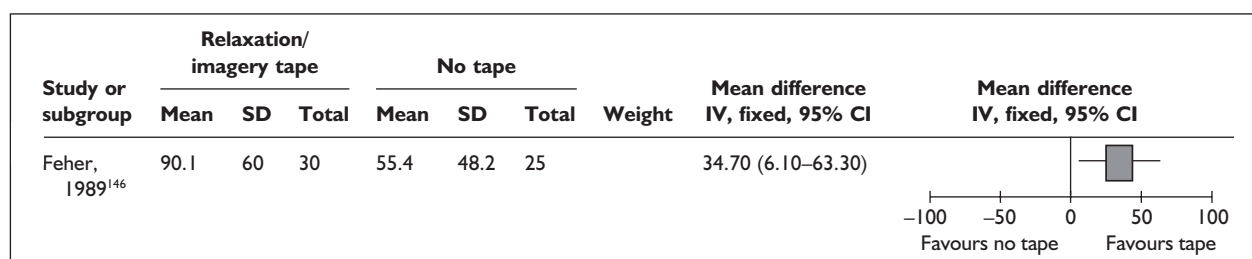


FIGURE 22 Relaxation imagery tape vs no tape: mean milk volume.

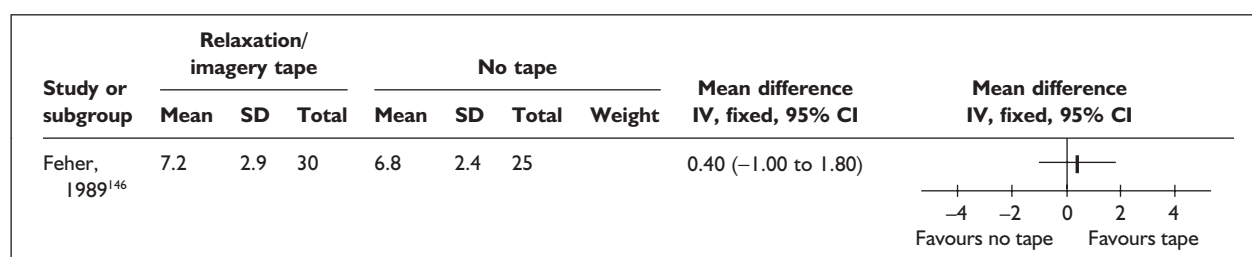


FIGURE 23 Relaxation imagery tape vs no tape: fat content.

**TABLE 8** Massage and pumping: milk yield per expression. Data from Jones *et al.*, 2001<sup>114</sup>

Intervention	Milk yield per expression
Massage with sequential pumping	78.71 (95% CI 85.19–72.24)
Massage with simultaneous pumping	125.08 g (95% CI 140.43–109.74)
No massage with sequential pumping	52.32 g (95% CI 56.57–46.07)
No massage with simultaneous pumping	87.69 g (95% CI 96.80–78.57)

Milk volume was greater after TT than after mock TT or no treatment ( $p < 0.05$ ).

The author noted that the large standard deviations reflect the large inter-participant variability. There were no significant differences in the fat content of the breastmilk expressed after each treatment.

### Secondary outcomes

#### Clinical/health outcomes

In the study of oxytocin nasal spray,<sup>144</sup> no adverse effects were recorded. In the metoclopramide study<sup>116</sup> the mean metoclopramide level found in milk from 14 intervention group mothers was  $44.8 \pm 20.4$  ng/ml, stated to be similar to levels found in studies of term women. The authors calculated maximum exposure to metoclopramide would be about 3% of the recommended daily dosage for children. In the domperidone study<sup>123</sup> domperidone levels were tested on day 5 and the milk:serum ratio was found to be 0.4. The authors state this is relatively low and much lower than metoclopramide. Mean (SD) serum prolactin on day 5 ( $\mu\text{g/l}$ ) was 119.3 (97.3) in the intervention group versus 18.1 (14.7) in the control group ( $p = 0.008$ ). Differences found between the groups in serum prolactin at baseline and 3 days after the last dose were not statistically significant. No side effects of domperidone were detected for mothers or infants in this small study. In the study of human growth hormone (hGH),<sup>133</sup> plasma concentrations of growth hormone, measured 24 hours after the last hGH injection, did not change significantly

after hGH therapy or placebo. In this small study, no adverse effects with hGH treatment were seen in mothers or infants.

#### Process outcomes

In the two UK studies with mothers of recently born preterm infants, the mean number of expression sessions per day was 3.5 in Fewtrell *et al.*<sup>144</sup> and 5.2 in Jones *et al.*<sup>114</sup> In both studies this was below the rate specified in the study protocol.

Two of the studies that included older preterm infants also report this outcome. The mean frequency of pumping (SD) was 4.5 (2.2) times per day before and during Mersmann's study.<sup>148</sup> In the study of hGH,<sup>133</sup> all mothers in both the groups were consistently expressing from both breasts 5–6 times daily before and during the study.

#### Psychosocial outcomes

Twenty-eight mothers in the oxytocin study,<sup>144</sup> 55% of those randomised, expressed a strong opinion on whether they had the active spray or placebo. Of twenty-two who were convinced they had the active spray, nine had the placebo; of six who thought they had the placebo, one had the active spray.

Nine of the 69 mothers (13%) randomised in the metoclopramide study<sup>116</sup> stopped breastfeeding in the first week. Their reasons included 'too little milk', 'too much stress' and 'too busy'.

In the study of the relaxation/imagery tape,<sup>146</sup> mothers expressed many positive responses to

**TABLE 9** Volume of milk expressed after therapeutic touch (TT), mock TT and no treatment. Data from Mersmann, 1993<sup>148</sup>

Intervention	Milk volume (ml) [SD], (median) and range
TT	59.9 [53.9] (47) 5–200
Mock TT	49.6 [49.0] (38) 4–220
No treatment	47.3 [52.6] (32) 4–220

the tape and no strong negative reactions. In the crossover study of breast massage,<sup>114</sup> all the mothers valued massage and many of those who were randomised to use massage on days 1 and 2 were reluctant about not using it on days 3 and 4. In the crossover study of TT, mothers were asked whether the first or second treatment they received was better. There were no differences between the groups.

## Results from other study designs

No studies of additional interventions to enhance milk production that used other study designs were identified.

## Interventions to support optimal nutritional intake from breastmilk

Three primary studies examining interventions related to optimising nutritional intake from breastmilk were identified. As detailed in *Table 10*, two studies were undertaken in the USA,<sup>20,145</sup> and one in Nigeria.<sup>140</sup> Two were RCTs,<sup>140,145</sup> and one was a concurrent comparison.<sup>20</sup>

## Results from RCTs

Two RCTs were identified<sup>140,145</sup> (*Tables 57* and *58* in Appendix 4.1).

### Characteristics of participants

One US trial<sup>145</sup> recruited English-speaking mothers having a preterm infant, 31–36 weeks' gestation, maintaining lactation during their stay in NICU and with the intention of breastfeeding post discharge. The Nigerian trial<sup>140</sup> recruited healthy preterm infants of gestational age < 37 weeks, with birthweights between 1000 and 1500 g.

Mothers were mainly older, primiparous, married and Caucasian in the US study.<sup>145</sup> Amali-Adekwu *et al.*<sup>140</sup> reported that infants of mothers who were HIV positive were excluded. In both trials infants were defined as 'healthy'.

### Characteristics of interventions

One trial assessed the effect of selective hindmilk feeding on the growth of very low birthweight preterm infants.<sup>140</sup> The infants were stratified by birthweight and gestational age, and received either hindmilk or composite milk (both foremilk and hindmilk), via intermittent gavage feeds following 4 days of established enteral feeds. Each infant was fed for 14 days after which infants in the experimental group reverted to composite milk until discharge.

The other trial<sup>145</sup> assessed infant milk intake by performing in-home measurement of weight pre- and post-feed measured at four time points: at discharge and at 1, 2 and 4 weeks post discharge. Extra milk feeds were given if required but type was not specified. Data were collected via questionnaire on breastfeeding history, infant feeding patterns up to 4 weeks post discharge, concerns about breastfeeding post discharge, and breastfeeding goals. A final questionnaire was completed on mothers' perceptions of the in-home measurement of milk intake.

### Outcome assessment

One study<sup>140</sup> reported outcomes for milk production and milk quality (lipid concentration and calorific value). Fat concentration was estimated daily by creatocrit measurement and the corresponding calorific values measured. Daily weight and weekly occipitofrontal circumference and recumbent length were measured. Peripheral blood samples were taken weekly to assess serum bicarbonate.

**TABLE 10** Included studies for 'interventions to support optimum nutritional intake from breastmilk'

Primary paper	Study design (n analysed) <sup>a</sup>	Country
Amali-Adekwu 2007 <sup>140</sup>	RCT (n = 68)	Nigeria
Hurst 2004 <sup>143</sup>	RCT (n = 31)	USA
Griffin 2000 <sup>20</sup>	Concurrent comparison (n = 26)	USA

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

In Hurst,<sup>145</sup> a breastfeeding history outcome was obtained from routinely collected data. Infant weight gain was measured at discharge from neonatal care, and 1, 2 and 4 weeks post discharge. Feeding patterns, urination and stooling were recorded from time of discharge to 4 weeks post discharge. For the intervention group the volume of milk intake was measured by test weighing. Milk intake for the control group was assessed using clinical indexes and infant behaviour. Concerns about breastfeeding were assessed at discharge and at 1, 2, and 4 weeks post discharge, and a breastfeeding goal questionnaire was completed at discharge. At the final post discharge visit mothers completed a questionnaire.

#### **Methodological quality of included trials**

Both RCTs<sup>140,145</sup> were considered to be 'poor' quality. Serious caution is warranted in interpretation of the results of these trials. Details of the quality rating for each trial are provided in *Table 81* in Appendix 5.

#### **Results from RCTs**

##### **Primary outcomes**

##### **Hindmilk vs composite breastmilk feeding**

In the study of hindmilk feeding, energy values for hindmilk were reported as  $3.73 \pm 0.5$  kJ/ml versus composite milk  $2.8 \pm 0.38$  kJ/ml ( $p = 0.001$ ), with creatatocrit (%)  $9.23 \pm 1.89$  for hindmilk versus  $5.73 \pm 1.4$  for composite milk.<sup>140</sup> Caution is required in interpretation of these findings due to the lack of reporting of complete data.

##### **Test weighing of infant intake post discharge**

There were no differences in breastfeeding outcomes in this trial.<sup>145</sup>

Findings should be interpreted with caution due to the poor quality of the trial.

##### **Secondary outcomes**

##### **Hindmilk vs composite breastmilk feeding**

Amali-Adekwu *et al.*<sup>140</sup> reported that weight gain was significantly higher in both SGA and appropriate for gestational age (AGA) infants fed on hindmilk than in controls fed with composite milk. Based on mean and SD data reported, SGA infants receiving hindmilk were calculated to have experienced significantly higher daily weight gain compared with SGA infants receiving composite milk (I:  $12.9 \pm 11.0$  g/kg, C:  $5.0 \pm 17.4$  g/kg;  $p = 0.001$ ).

There was also a positive correlation between rate of weight gain and lipid measurements of the breastmilk in both the SGA and AGA groups. Authors reported no significant differences in the occipitofrontal head circumference and length increments of any groups but presented no data.<sup>140</sup>

Hurst<sup>145</sup> reported no significant differences for change in weight or weight gain at any time points. Both comparison groups expressed concerns related to infant weight gain, quantity of milk consumed at each feed and concerns of infant getting enough from the breast. By week 1 post discharge, the main concerns were the adequacy of milk (intervention group) and the quantity of milk consumed (control group). The majority of the intervention group reported that they found it helpful to undertake the pre- and post-feed weighing of their infants although one-third of the mothers stated it made them feel nervous.

No trials reported cost-effectiveness data for the intervention.

#### **Results from other study designs**

One concurrent comparative study was identified evaluating interventions related to mothers' involvement in measuring breastmilk quality<sup>20</sup> (*Table 59* in Appendix 4.1).

##### **Characteristics of participants**

This study was conducted in the USA<sup>20</sup> among mothers who were expressing and when creatatocrit measurements were clinically indicated in the management of the infant's nutritional plan. There was a diverse distribution of mothers in relation to maternal age, occupation and income level reported. Of the 26 participants, 12 (46%) were white, 9 (35%) African American, and 5 (19%) Hispanic.

No information was reported for infant characteristics.

##### **Characteristics of intervention**

Mothers were taught to measure the fat content of their own expressed breastmilk using the creatatocrit (CRCT) technique<sup>20</sup> by one of two instructional registered nurses using a standardised teaching tool. The comparison group was formed of registered nurses who conducted the same procedure using a centrifuge located in an adjacent

room. All CRCTs were performed within 30 minutes of milk expression.

### Outcome assessment

Griffin *et al.*<sup>20</sup> reported the length of time taken to teach mothers the technique and the accuracy of the mothers' measurements compared with registered nurses. After practising the CRCT for approximately 72 hours, one of two validating registered nurses performed simultaneous CRCTs on the same breastmilk sample. To standardise these differences with respect to the actual CRCT value the percentage error in each mother's measurement was calculated by dividing the absolute difference between the registered nurse's and mother's CRCT by the registered nurse's mean CRCT.

### Methodological quality of the included study

This study was rated 'good' quality overall.<sup>20</sup> Details of the quality rating for this study are provided in Table 82 in Appendix 5.

### Effectiveness of the intervention

#### Primary outcomes

This comparison study<sup>20</sup> reported that mothers' CRCT measurements were highly accurate when compared with the validating registered nurses. The differences between the mothers' and registered nurses' measures were compared using mean, standard deviation, minimum and maximum differences, mean absolute differences, the percentage of difference of 0.5% or < 1% and the percentage of error. The percentage error values between the two groups were: ≤0.5% error, 50%; < 1.0% error, 84.6%, with a percentage error between mothers and registered nurses of 6.8%, showing a high degree of accuracy between the mothers' and registered nurses' measures. When standardised, the percentage of error in the mothers' measurements was lower than those between the two validating registered nurses performed during a pilot study (6.8% errors for mothers compared with 10.51% of error by the validating registered nurses). No association was found between magnitude of error and maternal age, years of formal education, or household income.

#### Secondary outcomes

The mean time for teaching this technique was reported as 23.6 minutes.<sup>20</sup> Mothers reported that performing CRCTs was easy to learn and simple to carry out, and they felt they were making a difference and influencing their infant's outcomes.

Cost-effectiveness data were not reported.

## Breastfeeding education and support interventions

A total of six primary studies and two systematic reviews evaluating breastfeeding support interventions were identified. As detailed in Table 11, three primary studies were included in at least one of the three systematic reviews. Four of the six studies were conducted in the USA, one in Canada<sup>126</sup> and one in the Philippines.<sup>117</sup>

### Results from RCTs

Three RCTs of breastfeeding education and support interventions were identified (see Tables 60–62 in Appendix 4.1).

#### Characteristics of participants

Two of the studies were performed in industrialised country settings including one in the USA<sup>143</sup> and one in Canada.<sup>126</sup> The remaining study was conducted in the Philippines.<sup>117</sup>

One study<sup>143</sup> took place and another<sup>117</sup> began in hospitals that had received Baby Friendly accreditation; the report of the third study does not mention Baby Friendly accreditation.<sup>126</sup>

All three studies included mothers who intended to breastfeed, with that of Merewood *et al.*<sup>143</sup> requiring in addition that mothers should be eligible to breastfeed in accordance with American Academy of Pediatrics Work Group on Breastfeeding (1997)<sup>60</sup> guidelines. Age and parity of the mothers in the study by Merewood *et al.*<sup>143</sup> were not reported. All spoke English or Spanish, over 70% were not US-born, 69% were African American and over 50% were on Medicaid. Five hundred and seventy-seven mother–infant pairs were assessed for eligibility and 452 (78%) were excluded for not meeting eligibility criteria, 'many' because of illicit maternal drug use. The study in the Philippines<sup>117</sup> specified that mothers should be primiparous and at least 18 years old, and excluded mothers taking medications that may compromise breastfeeding and mothers who were not going to stay in the study area with their infants for 6 months. The included mothers had a mean age in the early twenties; almost all had secondary or college education; 70% were living with a partner and just over 30% worked or studied outside the home. The mothers in Canada<sup>126</sup> were older, with a mean age just under 30 years, and 40% had other



**TABLE 11** Included studies for 'Breastfeeding education and support interventions'

Primary paper	Study design (n analysed) <sup>a</sup>	Inclusion in existing systematic review	Country
Agrasada 2005 <sup>117</sup>	RCT (n = 204)	Edmond 2006 <sup>155</sup>	Philippines
Gonzalez 2003 <sup>166</sup>	Before/after (n = 350)	McInnes 2006 <sup>161</sup>	USA
Merewood 2006 <sup>143</sup>	RCT (n = 85)	No	USA
Pereira 1984 <sup>153</sup>	Before/after (n = 402)	No	USA
Pinelli 2001 <sup>126</sup>	RCT (n = 128)	Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	Canada
Senn 2004 <sup>152</sup>	Before/after (n = 50)	No	USA

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

children. All were English speaking and almost all were classified as social class I or II. Seventy percent were living with a partner, and fathers were included in this study.

Infant characteristics varied widely between the three studies. Only VLBW infants (< 1500 g) were included in the Canadian study;<sup>126</sup> they were born at a mean (SD) of 29 (3) weeks. The study by Merewood *et al.* in the USA<sup>143</sup> included infants with a mean birthweight of 1877 g (range 682–3320 g) and a mean gestational age of 32.7 weeks (range 26–37 weeks); 30% of the infants were born at < 32 weeks' gestational age and 70% at ≥ 32 weeks. Agrasada's study in the Philippines<sup>117</sup> included LBW infants (< 2500 g) born vaginally at term (37–42 weeks). All the studies included only singleton infants and two specifically excluded infants with congenital abnormalities.<sup>126,143</sup>

### Characteristics of interventions

The intervention in the study of Pinelli *et al.* in Canada<sup>126</sup> was supplemented structured breastfeeding counselling (SSBC) for both parents, from within 72 hours of the birth of their VLBW infant (n = 64). SSBC involved viewing a video on breastfeeding for preterm infants, individual counselling by the research lactation consultant (not a member of the hospital staff), weekly personal contact in the hospital and frequent postdischarge contact (type of contact unspecified) through the infant's first year or until breastfeeding was discontinued. The control group (n = 64) were allocated to Conventional Hospital Breastfeeding Support (CHBS), standard care at the time of the study. CHBS included contact with the regular

hospital staff (nurses, nutritionists, neonatal nurse practitioners, physicians), during the period of hospitalisation only. Only a limited number of staff had any formal education in lactation or breastfeeding support, and no specialised breastfeeding clinic was available to parents in the hospital. Standard care in the community was not described.

The intervention in the study of Merewood *et al.* in the USA<sup>143</sup> was peer counsellor support for mothers, from within 72 hours of the birth of their preterm (26–37 weeks' gestation), otherwise healthy infant (n = 53). The five peer counsellors were women with breastfeeding experience, drawn from the local community of mixed ethnic backgrounds; two had been teenage mothers. They were employed for this work, and two were also employed as lay childbirth assistants at the study hospital. Peer counsellors were trained at a 5-day breastfeeding course. They also had training at the hospital about NICU procedures and breastfeeding techniques, and attended regular, mandatory breastfeeding training days for maternity staff throughout their employment. After initial contact, the peer counsellor was in contact with the mother on a weekly basis for 6 weeks. After the infant was discharged from hospital, contact was by telephone unless the mother went to hospital. The control group (n = 55) was allocated to standard care. The study hospital had Baby Friendly accreditation, and standard care included staff who were highly trained in lactation management, access to three breastfeeding classes per week, referrals to the lactation consultant when needed, use of a breast pump in the hospital and a free, high-grade

electric breast pump for home use if the mother's insurance did not pay for a pump. No other community support components of standard care were reported.

In Agrasada's study in the Philippines<sup>117</sup> there were three study groups; breastfeeding counselling from community-based peer counsellors, childcare counselling from community-based peer counsellors, and no peer counselling. In all three groups, mothers who vaginally delivered term LBW infants were sent to the rooming-in ward. Term LBW infants with birthweights < 2 kg were observed in the NICU for 12–24 hours. The paper is not explicit about management of term LBW infants with birthweights of 2–2.5 kg. While separated from their mothers, the infants received (by dropper) fresh expressed breastmilk (EBM) donated by lactating mothers on the ward. As soon as their condition was stable, the infants joined their mothers on the rooming-in ward. Although the authors state the study hospital had been assessed as 'Baby Friendly', they also indicate that in this rooming-in ward, no hospital staff or volunteers were tasked to educate or assist mothers with breastfeeding. Mothers were discharged 24–72 hours post partum, breastfeeding exclusively. They were informed of their group assignment as they were leaving hospital and were asked to come to the hospital clinic for the usual seven infant visits, at 2 and 4 weeks then monthly until 6 months, at which study measures were taken. No other community support components of standard care were reported.

The peer counsellors in Agrasada's study<sup>117</sup> were 14 women health volunteers (age 22–50 years) with similar formal education to the mothers, who were willing to do home visits. They undertook 40 hours counselling training. Six were trained by a maternal child health-care specialist and became childcare counsellors (for CC group), and eight with positive personal breastfeeding experience were trained by a certified lactation specialist and became breastfeeding counsellors (for BC group). They were not salaried; they received local transport costs during training and home visits. Eight home visits were scheduled, at infant age 3–5, 7–10 and 21 days, then monthly up to 5.5 months. In the breastfeeding counselling intervention (BC,  $n = 68$ ), peer counsellors informed mothers of the benefits of exclusive breastfeeding to 6 months, and assisted mothers in preventing and managing breastfeeding problems. In the childcare counselling intervention (CC,  $n = 67$ ), peer counsellors assisted mothers on infant care

and increasing mother–infant interaction using activities such as infant massage and smile therapy. In the control group (C,  $n = 69$ ), there was no input from peer counsellors.

### **Outcome assessment**

The main outcome measure in the Canadian study of VLBW infants<sup>126</sup> was duration of breastfeeding. Proportions of intake from breastmilk/breastfeeding at term and up to 1 year are reported. It is implied but not stated that the time points up to 1 year are post term and not post birth. This study also reported aspects of mothers' breastfeeding experiences in NICU (age after birth that pumping started, frequency and duration of pumping, amount pumped, age when infant first put to the breast, frequency of breastfeeding) and at home (breastfeeding problems, what resources mothers used to solve breastfeeding problems, reasons for discontinuing breastfeeding).

The main outcome measure of the study conducted in the USA<sup>143</sup> was any breastmilk feeding at 12 weeks post partum. Odds of all the mothers, and of African American mothers, giving any, mostly or all breastmilk are presented. This study also reported process outcomes (percentage of documented cases in which the peer counsellor discussed pumping, helped the mother to pump, breastfeed, perform kangaroo care; accompanied the mother to NICU; and whether contact with the mother took place in person by telephone).

The main outcome measure of the study of term LBW infants in the Philippines<sup>117</sup> was the proportion of mothers breastfeeding exclusively from 2 weeks to 6 months. This study also reported any breastfeeding, infants' mean weight-for-age, infants' rates of diarrhoea, and mothers' views of the programme, as well as mothers' breastfeeding knowledge and intentions as assessed at the start of the study.

### **Methodological quality of included trials**

Two studies<sup>117,126</sup> were rated as 'good' quality overall. One study<sup>141</sup> was rated as 'moderate' quality (see *Table 83* in Appendix 5).

### **Effectiveness of interventions**

#### **Primary outcomes**

Complete outcome data for all those originally enrolled were provided in or could be calculated from two papers.<sup>117,126</sup> Individual relative risk estimates, calculated on an ITT basis, are presented in forest plots for primary outcomes from these two studies, which both received a 'good' overall

quality rating (Figures 24 and 25). The report of the study by Merewood *et al.*,<sup>143</sup> which was quality-rated moderate, lacked the data needed for estimating relative risks.

### Breastfeeding at term

In the study of breastfeeding peer support vs childcare peer support vs no peer support (Agrasada 2005<sup>117</sup>) all the participants were exclusively breastfeeding at term, when the peer support interventions began. In the study of professional support vs standard care (Pinelli *et al.* 2001<sup>126</sup>) there were no differences in intake of breastmilk between the groups at term (see Figure 24).

### Any breastfeeding at 12 weeks

In Agrasada's study, significantly more mothers were breastfeeding at 12 weeks in the breastfeeding peer support group than in the no peer support group (see Figure 25). The numbers of mothers in the childcare peer support group who were breastfeeding at 12 weeks was 36/67, very close to the numbers in the no peer support group.

In the study of professional support vs standard care (Pinelli *et al.* 2001<sup>126</sup>), there was no statistically significant difference between the groups in numbers of infants with any intake from breastfeeding or breastmilk at 12 weeks (see Figure 25).

In the study of peer support vs Baby Friendly standard care (Merewood *et al.* 2006<sup>143</sup>), the numbers randomised, excluded post randomisation and lost to follow-up for each study group were reported. A total of 23 were lost from the 108 randomised in this study (21.3%), with more lost from the intervention group (15/63, 24%) than from the control group (8/55, 14%). Relative risks might therefore have been different if calculated on an ITT/postrandomisation exclusions basis as we planned, compared with what they would have been if calculated on an available case basis, as were the odds ratios reported in the paper. However, numerators were not reported so relative risks could not be calculated.

Merewood *et al.*<sup>143</sup> reported on outcome for 38/53 participants in the peer counselling group and 47/55 in the Baby Friendly standard care group. At 12 weeks post partum, mothers with a peer counsellor were significantly more likely to provide milk than mothers without a peer counsellor (odds ratio 2.81; 95% CI 1.11–7.14;  $p = 0.01$ ). Among the subgroup of African American participants (30 in the peer counselling group and 29 in the Baby Friendly standard care group), Merewood *et al.*<sup>143</sup> reported that at 12 weeks, African American mothers with a peer counsellor were significantly more likely to provide milk than African American mothers without a peer counsellor (odds ratio 3.59; 95% CI 1.16–11.03;  $p = 0.03$ ).

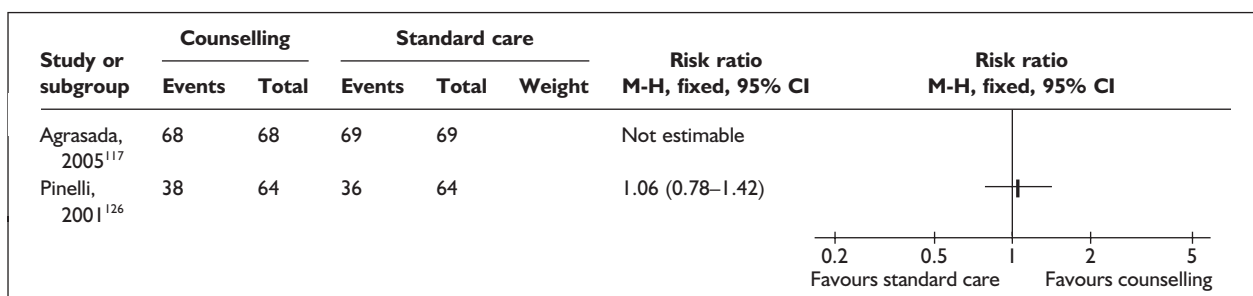


FIGURE 24 Counselling/support by professional or peer counsellor in hospital/at home: breastfeeding at term.

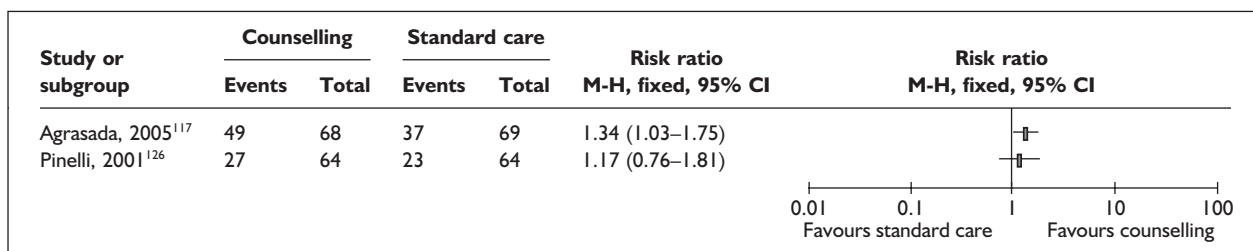


FIGURE 25 Counselling/support by professional or peer counsellor in hospital/at home: any breastfeeding at 12 weeks.

It should be noted that the postconception age of the infants at 12 weeks' post partum varied in this study.

**Any breastfeeding at 24 weeks**

In Agrasada's study, significantly more mothers were breastfeeding at 24 weeks in the breastfeeding peer support group than in the no peer support group (Figure 26). The numbers of mothers in the childcare peer support group who were breastfeeding at 24 weeks was 21/67, very close to the numbers in the no peer support group.

In Pinelli's study there was no significant difference between the groups in numbers of infants with any intake from breastfeeding or breastmilk at 24 weeks (see Figure 26).

**Exclusive breastfeeding from birth to 6 months**

In Agrasada's study<sup>117</sup>, significantly more mothers breastfed exclusively from birth to 6 months in the breastfeeding peer support group (32/68) than in the no peer support group (0/69) (Figure 27). Two of the 67 mothers in the childcare peer support group breastfed exclusively from birth to 6 months.

**Amount of milk pumped for hospitalised infants**

There was no significant difference between the groups in mean amount of milk pumped by mothers for their hospitalised infants in Pinelli's

study (Figure 28). The range of milk volumes obtained was wide (4–350 ml in the breastfeeding counselling group and 6–200 ml in the standard care group).

**Secondary outcomes**

**Clinical/health outcomes**

Agrasada (2001)<sup>117</sup> found no significant differences between the groups in mean weight for age at birth or 6 months. Rates of diarrhoea were halved in the breastfeeding peer counselling group (15%) compared with the other two groups. There were no infant deaths among the study participants. Clinical/health outcomes were not reported by Merewood *et al.* (2006)<sup>143</sup> or Pinelli *et al.* (2001).<sup>126</sup>

**Process outcomes**

Pinelli *et al.*<sup>126</sup> found no significant differences between the groups in age after birth when pumping started (mean 28 days, range 1–72 days); frequency of pumping in NICU [mean 6 (SD 2) per 24 hours, range 1–20]; length of pumping sessions in NICU (mean 18.5 minutes, range 5–45); age when infant first put to the breast (mean 25 days, range 0–102) or frequency of breastfeeding per day in NICU (mean 3.5, range 1–9). Post discharge, more than 50% of mothers in both groups experienced breastfeeding problems including sore nipples, fatigue, not enough milk, infant not gaining weight and infant not interested in breastfeeding. The only significant difference between the groups was that more mothers in the

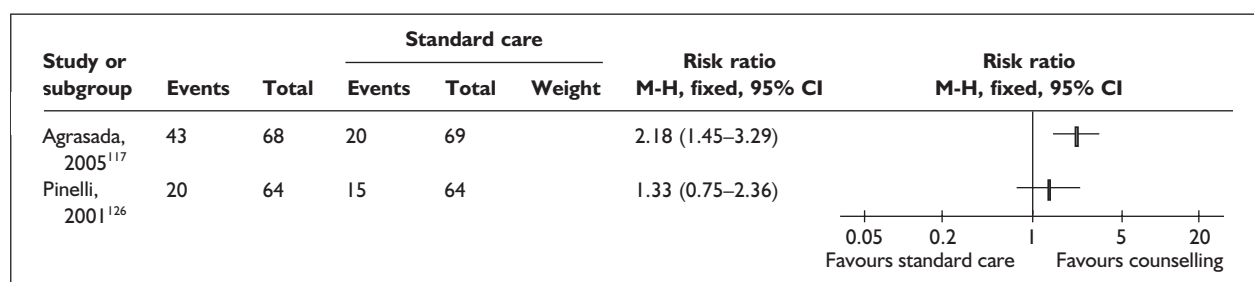


FIGURE 26 Counselling/support by professional or peer counsellor in hospital/at home: any breastfeeding at 24 weeks.

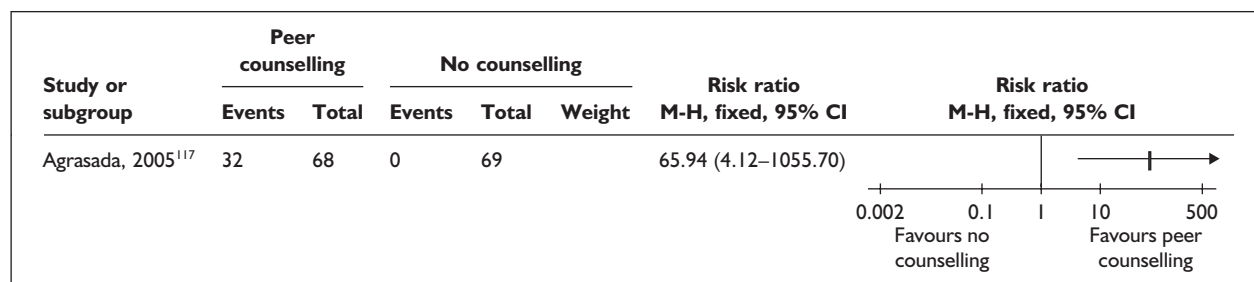
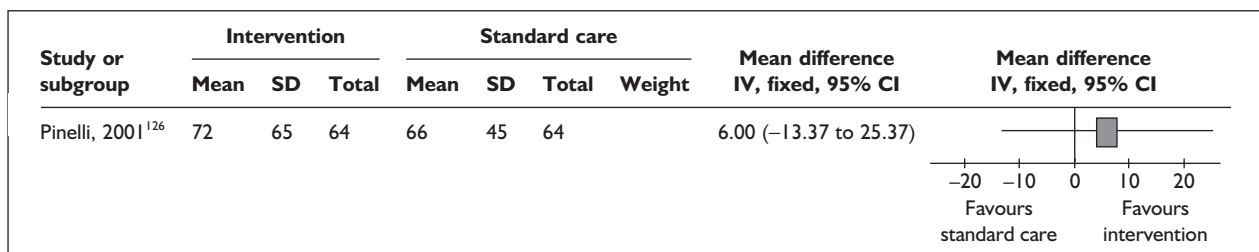


FIGURE 27 Counselling/support by peer counsellor at home: exclusive breastfeeding from birth to 6 months.



**FIGURE 28** Counselling/support by professional counsellor in hospital: amount of milk pumped (ml).

intervention group reported the infant was not gaining weight ( $p = 0.05$ ). At 6 months the main reason for stopping breastfeeding was 'not enough milk'; at 1 year the main reason was 'infant not interested in breastfeeding'. Merewood *et al.*<sup>143</sup> reported on peer counsellor's field records for 43/48 (90%) of the intervention group. The peer counsellor discussed pumping in all documented cases; accompanied the mother to NICU in 72.1%; helped the mother to pump in 72.1%; and helped the mother to breastfeed, perform kangaroo care or both in 30.2%. After 4 weeks, 37.2% of the infants remained in NICU, and 81.3% of mothers of these infants were seen in person by the peer counsellor in NICU. Other contacts were by telephone. Agrasada<sup>117</sup> did not report process outcomes.

#### Psychosocial outcomes

Pinelli *et al.*<sup>126</sup> reported mothers using a wide variety of breastfeeding resources for solving breastfeeding problems at home, including health professionals, books, friends and family. The most used resource over all time periods was the lactation consultant. This included the research lactation consultant in the study group and community lactation consultants in both groups. At exit interview, mothers in Agrasada's study<sup>115</sup> who had counsellors stated they were satisfied with the programme. Mothers who had breastfeeding counsellors said the counsellor was the person who had influenced their feeding decisions the most. Mothers in the other two groups said the physician had influenced their feeding decisions the most. Merewood *et al.*<sup>143</sup> did not report psychosocial outcomes.

#### Cost-effectiveness outcomes

None were reported from these studies.<sup>117,126,143</sup>

### Results from other study designs

Three before/after studies were identified<sup>152,153,166</sup> (see Tables 63–65 in Appendix 4.1). Two of these collected prospective data for the intervention

group<sup>152,153</sup> and one collected retrospective data for both groups.<sup>166</sup>

All three studies were undertaken in the USA. That by Gonzalez *et al.*<sup>166</sup> took place in a NICU with approximately 700 admissions per year, with infants who were mainly preterm (< 37 weeks' gestation) or low birthweight ( $\leq 2500$  g). A survey prior to the study done by Pereira *et al.*<sup>153</sup> showed 17% of infants in that study unit were breastfed from birth and half of these were exclusively formula fed by the time of discharge. The rural NICU in which the study of Senn<sup>152</sup> took place treated infants with birthweight  $\geq 750$  g who did not require surgery. In 1997–8, 49.7% of infants born  $\leq 34$  weeks' gestation received breastmilk at least once.

#### Characteristics of participants

Gonzalez *et al.*<sup>166</sup> examined randomly selected records of infants in NICU during 6 months before ( $n = 175$ ) and 6 months after ( $n = 175$ ) initiation of the intervention. No significant differences between the groups were found for sociodemographic or clinical factors, including mother's age, ethnicity, infant gender, Apgar scores at 5 minutes, or length of stay. Sixty-seven percent of the infants were preterm and/or low birthweight.

Pereira *et al.*<sup>153</sup> examined records of infants in NICU during two 6-month periods before ( $n = 192$ ) and after ( $n = 210$ ) initiation of the intervention, and gave a questionnaire to mothers who had received the intervention. The groups of mothers were comparable and mainly white, 20–30 years old and privately insured. Infant characteristics were not reported.

Senn<sup>152</sup> recruited 25 mothers of infants in NICU and matched them with 25 historical controls. The mothers were on average in their mid- to late twenties, had public insurance or no insurance, more than a high-school education, and were married. Around half were multiparous, with breastfeeding experience not reported. Mothers

of twins or triplets were invited to participate, with one infant chosen randomly for inclusion in the analyses. The only significant difference found between the groups was for race: all the intervention group were white, and seven of the 25 historical controls (28%) belonged to minority ethnic groups ( $p < 0.01$ ). Infants were relatively healthy, born at around 33 weeks' gestation and weighing around 2000 g at birth, with an average hospital stay of about 2.5 weeks.

### **Characteristics of interventions**

The intervention in the study by Gonzalez *et al.*<sup>166</sup> was the introduction of an International Board Certified Lactation Consultant support service within the NICU. The lactation consultant contacted mothers within 24 hours of their infants' admission to NICU and counselled mothers regarding the benefits and options for providing her milk to the infant. If the mother chose to provide her milk, a feeding plan was developed. Lactation consultants were available from 7 am to 6 pm to answer questions and assist with pumping. A telephone message service was available after hours. Standard care on the study unit was not described.

The intervention in Pereira's study<sup>153</sup> was the introduction of a programme of breastfeeding support by trained, community-based volunteer counsellors for mothers intending to breastfeed. Mothers were informed of the availability of counselling by NICU staff. The programme coordinator contacted the mother and assigned a counsellor living nearby. Seventeen peer counsellors who had successfully breastfed their sick infant and had received certification and orientation to the neonatal unit were available. Counselling included empathy and emotional support as well as collection, home storage and transport to hospital of expressed breastmilk; transition from tube feeding to breastfeeding; maternal diet during lactation and medications excreted in breastmilk. The paper implies but does not state that the counsellors made home visits. Telephone counselling was provided as needed. Standard care on the study unit and following discharge was not described.

The intervention in Senn's study<sup>152</sup> was the Lactation Education Breastfeeding Program. This programme had two core sessions, designed to be interesting, fun and interactive. Participants were given a \$25 Wal-Mart gift card for each session they attended. In Session 1, mothers had an individual meeting with the lactation consultant shortly after the birth. Topics included pumping,

storing and transporting breastmilk, hand washing, use and cleaning of the pump, how long and how frequently to pump and time for questions. Mothers who wanted to feed directly from the breast could meet the lactation consultant for an additional session when the infant was mature enough for this. In Session 2, mothers were invited to a weekly group educational session led by the lactation consultant, with group activities covering infant and maternal benefits of breastfeeding and social support for breastfeeding. Mothers created a list of people who could give them informational, tangible and emotional support with breastfeeding, and were given a list of community breastfeeding resources. Standard care on the study unit is not described.

### **Outcome assessment**

Gonzalez *et al.*<sup>166</sup> reported percentages of infants given their own mother's milk (OMM), and factors associated with receiving OMM feedings. Pereira *et al.*<sup>153</sup> reported the in-hospital breastfeeding rate, duration of breastfeeding and mothers' views of the programme. Senn<sup>152</sup> reported how many infants received breastmilk at least once; received breastmilk within 2 days of feeding initiation; the mean percentage of days on which infants received breastmilk; on days receiving breastmilk, the mean percentage of feedings of breastmilk they received; ever breastfed; the mean percentage of days breastfed; on days breastfed, the mean percentage of feedings breastfed; breastmilk at discharge; mean age at discharge; and the intervention group mothers' perceptions of breastfeeding benefits, barriers and self-efficacy before and after the intervention.

### **Methodological quality of included studies**

Two studies were rated as 'moderate' quality.<sup>153,166</sup> One study was rated as 'poor' quality.<sup>152</sup> Details of the quality ratings for each study are provided in Table 84 in Appendix 5.

### **Effectiveness of interventions**

#### **Primary outcomes**

Gonzalez *et al.*<sup>166</sup> reported that 31% of infants before the intervention, compared with 47% in the lactation consultant group, ever received their own mother's milk ( $p = 0.002$ , OR 2.0, 95% CI 1.3–3.0). At hospital discharge, 23% of infants before the intervention were receiving any breastmilk, compared with 37% in the lactation consultant group ( $p = 0.004$ , OR 2.0, 95% CI 1.2–3.2).

Pereira *et al.*<sup>153</sup> found the in-hospital breastfeeding rate before the intervention was 17%, compared with 30% after the intervention ( $p < 0.01$ ). Duration

of breastfeeding (mean, in days) was 41.6 (SEM 9.4) before the intervention, compared with 134 (SEM 12.9) after the intervention ( $p < 0.001$ ).

Senn<sup>152</sup> found no differences between the groups in infants receiving breastmilk at least once, those ever breastfed, and those receiving breastmilk at discharge.

### Secondary outcomes

#### Clinical/health outcomes

None were reported from these studies.<sup>152,153,166</sup>

#### Process outcomes

Using logistic regression analysis, Gonzalez *et al.*<sup>166</sup> found that factors significantly associated with giving own mother's milk to infants in the NICU were lactation consultant care ( $p = 0.002$ ), white ethnicity ( $p < 0.001$ ), male gender of the infant ( $p = 0.04$ ), higher 5-minute Apgar score ( $> 7$ ) ( $p = 0.003$ ), and a stay in NICU greater than 7 days ( $p = 0.007$ ).

#### Psychosocial outcomes

The questionnaire sent to mothers receiving the intervention in Pereira's study<sup>153</sup> had a 93% response rate (59/64). Overall, 61% of respondents ranked the programme 'very beneficial' and 39% found it 'somewhat beneficial'. No respondent regarded counselling as 'non-beneficial'.

#### Cost-effectiveness outcomes

None were reported from these studies.

## Staff training interventions

Two studies evaluating staff training interventions were identified. As detailed in *Table 12*, one study was undertaken in the UK<sup>81</sup> and one in the USA.

Neither of these studies was included in a previous systematic review.

### Results from RCTs

No randomised trials evaluating the effect of staff training on breastfeeding outcomes were identified.

### Results from other study designs

Two before/after studies of training interventions for health-care professionals were identified<sup>81,149</sup> (see *Tables 66* and *67* in Appendix 4.1).

#### Characteristics of participants

The two studies were conducted in industrialised countries, one in the UK<sup>81</sup> and one in the USA.<sup>149</sup>

One study<sup>81</sup> delivered an education intervention to health-care professionals working within the neonatal unit, including eight neonatal-trained midwives, eight neonatal-trained paediatric nurses, 12 registered nurses, three paediatric nurses, two paediatric house officers, and one paediatric registrar. No data were given related to health-care professional characteristics other than professional status. All mothers included in the evaluation intended to breastfeed. No infant characteristics were reported.

Pineda<sup>149</sup> conducted an intervention that included an education package to health-care professionals including 75 nurses, three rehabilitation therapists, one nurse practitioner, two neonatologists, one respiratory therapist and five other health professionals. Mothers who received education and support in this intervention were comparable. There was a large proportion of mothers in both groups of low socioeconomic status (B: 77.5%; A: 70%). The infants were comparable for birthweight

**TABLE 12** Included studies for 'staff training interventions'

Primary paper	Study design (n analysed) <sup>a</sup>	Country
Jones 2004 <sup>81</sup>	Before/after Staff training (n = 88) <sup>a</sup> Mothers (n = 135) <sup>a</sup>	UK
Pineda 2006 <sup>149</sup>	Before/after Staff training (n = 34) <sup>a</sup> Mothers (n = 262) <sup>a</sup>	USA

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

(mean birthweight B: 1074 g and A: 1114 g) and estimated gestational age (mean B: 28.57 weeks and A: 28.7 weeks). Mean length of stay in hospital (B: 50 days and A: 54 days) and numbers of transfers to other hospitals (B: 43.2% and A: 32.7%) were also comparable.

### Characteristics of interventions

Jones *et al.*<sup>81</sup> designed an evidence-based programme of education describing preterm mammary physiology, milk expression and the establishment of preterm oral skills. This was taught in five separate modules, delivered by a neonatal breastfeeding coordinator, and took 10 hours to complete. Additional information was available via CD-ROM and video.

Pineda<sup>149</sup> developed an evidence-based educational initiative addressing areas relevant to the neonatal unit setting. Topics covered included benefits of and barriers to breastfeeding, the physiology of lactation, use of breast pumps, prefeeding interventions and interventions related to the readiness of the preterm infant to feed. The programme was completed by health-care professionals working within the neonatal unit either through self-study or by attendance at taught in-service days in the neonatal unit. It incorporated a pathway of care for providing support for new mothers. Nurses documented the education and support given to mothers at predefined times. Critical time points were: within 6 hours of birth, to issue and instruct in proper pumping and breastmilk storage; within 24 hours of birth, to ensure proper pumping and storage technique; on days 3–5, to ensure milk has come in and troubleshoot any problems, foster continued pumping and skin-to-skin care; first oral feeding, to ensure it is a breastfeeding session; and at 10 days, to monitor milk supply and make referrals as appropriate. An educational pamphlet designed specifically for mothers whose infant was admitted to NICU was also devised. This contained information about the benefits of breastfeeding, the expressing and storage of milk, prebreastfeeding strategies and cue-based breastfeeding behaviour of the infant.

### Outcome assessment

Jones *et al.*<sup>81</sup> reported educational outcomes for staff, as assessed by a pre- and post-test of knowledge. Following the development of a questionnaire, advice was sought from three experienced specialists and the package, including the pre- and post-test, was piloted on five trainee neonatal nurses. A total score of 85 was achievable. This study also reported changes in recording of

milestones achieved through the transition phases towards breastfeeding at discharge, including actions to promote each transition, as assessed by case note review of infant records.

Pineda<sup>147</sup> assessed outcomes by case note review and reported breastfeeding initiation, whether or not breastmilk was provided at discharge, and the proportion of hospital stay during which breastmilk was provided. The unit of allocation and analysis for this study was the mother and not the infant.

### Methodological quality of included studies

Both studies were assessed as moderate quality. Details of the quality rating for each study are provided in *Table 85* in Appendix 5.

### Effectiveness of the intervention

#### Primary outcomes

Jones *et al.*<sup>81</sup> reported on retrospective analysis of infants' notes for all admissions to the neonatal unit during a 3-month period prior to training and for an unspecified time after training (B: 135; A: 127). Expressed breastmilk was given to a higher proportion of infants following the intervention (B: 74/86, 86%; A: 72/74, 97%;  $p = 0.012$ ). There was a significant increase in the documentation of a problem-solving plan for milk expression (B: 2/84, 2%; A: 57/66, 86%;  $p < 0.0001$ ) and skin-to-skin contact (B: 15/46, 33%; A: 63/64, 98%;  $p = 0.001$ ). There was also a significant increase in cup feed offered (B: 53/82, 65%; A: 56/66, 85%;  $p < 0.006$ ) and infants put to the breast (B: 57/76, 75%; A: 65/69, 94%;  $p = 0.002$ ). A statistically significant increase in breastfeeding at discharge was not demonstrated (B: 49/73, 67%; A: 54/68, 79%;  $p = 0.1$ ).

Pineda<sup>149</sup> reported a comparison of VLBW infants admitted to the neonatal unit, 1 year prior to the intervention and 9 months after (B: 81; A: 54). There was a significant increase in the number of mothers who ever breastfed their infants while in hospital (B: 21/81; A: 24/54; OR 2.286; CI 1.1–4.75;  $p = 0.025$ ). The provision of breastmilk at discharge did not increase, and the multifaceted staff training intervention did not demonstrate a significant increase in breastmilk provided during hospitalisation.

#### Secondary outcomes

Jones *et al.*<sup>81</sup> conducted a pre- and post-test assessment to evaluate the effectiveness of the training package on health-care professionals' knowledge related to the topics covered in the programme.



Data for the pre- and post-test assessment on staff knowledge was available for 34/42 health-care professionals. A statistically significantly increased (median) score was demonstrated between the pre- and post-test results (maximum score of 85) (B: 32.5, range 9–39; A: 44.6, range 34–60.5;  $p = 0.001$ ). Authors have not adjusted for the independent effect of participating in the pre-test. The programme was positively evaluated by the participants. Skin-to-skin contact undertaken between the mother and infant increased significantly following the intervention (B: 5/46, 33%; A: 63/64, 98%;  $p = 0.0001$ ).

Pineda<sup>149</sup> reported that 88 (63%) of all neonatal health-care professionals (denominator data not provided) completed the educational programme. All achieved a post-test assessment of  $\geq 80\%$ . The independent effect of participating in the pre-test was not assessed. Nurses did not always comply with the established guidelines on the breastfeeding pathway and the educational booklet designed for the mother was not distributed consistently. Not all mothers were given their booklet on admission and some never received them (numbers not reported).

Cost-effectiveness data were not reported in either of these studies.

## Early hospital discharge with home support interventions

Two primary studies reported in three papers<sup>109,110,127</sup> evaluating early hospital discharge with home support interventions were identified. Both were conducted in industrialised countries,

namely New Zealand and Sweden. As detailed in *Table 13*, both primary studies were included in at least one of the three previous systematic reviews.<sup>155,160,161</sup>

## Results from RCTs

Both studies were RCTs<sup>109,110,127</sup> (see *Tables 68* and *69* in Appendix 4.1).

### Characteristics of participants

Both trials took place in industrialised settings and recruited infants in neonatal care with a gestational age of less than 37 weeks.<sup>109,110,127</sup> Twins were included in both the trial conducted in New Zealand (I: 29/148; C: 33/160)<sup>127</sup> and the trial conducted in Sweden (I: 5/45; C: 8/47).<sup>109,110</sup> The latter trial excluded triplets and quadruplets.<sup>109,110</sup>

The mean gestational age (weeks) of infants recruited was slightly lower in the study conducted in Sweden by Ortenstrand *et al.* (I: 31.4, SD 2.8; C: 32.0, SD 2.3)<sup>109</sup> than those recruited in the study conducted in New Zealand by Gunn *et al.* (I: 33.2, SD 2.3; C: 32.9, SD 2.5).<sup>127</sup> Similarly, mean birthweights (g) were slightly lower among infants in the Swedish study (I:  $1677 \pm 549$ ; C:  $1737 \pm 486$ )<sup>109,110</sup> than among infants in the New Zealand study (I: 2007, SD 503; C: 1970, SD 535).<sup>127</sup> Preterm infants of both low and very low birthweights were included.

The mean gestational age at discharge for infants in the New Zealand trial was 36.1 weeks (SD 1.5) for the intervention group and 36.4 (SD 1.2) for the control group.<sup>127</sup> It is important to note that statistically significant differences were reported between comparison groups

**TABLE 13** Included studies for 'early hospital discharge with home support interventions'

Primary paper	Study design (n analysed) <sup>a</sup>	Inclusion in existing systematic review	Country
Gunn 2000 <sup>127</sup>	RCT (n = 308)	Edmond 2006 <sup>155</sup> McInnes 2006 <sup>161</sup>	New Zealand
<sup>b</sup> Ortenstrand 2001 <sup>110</sup>	RCT (n = 88)	McInnes 2006 <sup>161</sup>	Sweden
<sup>b</sup> Ortenstrand 1999 <sup>109</sup>		<sup>c</sup> Edmond 2006 <sup>155</sup> Collins 2003 <sup>160</sup>	Sweden

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate postrandomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

b Ortenstrand 1999 and 2001 papers pertain to the same study.

c The Edmond 2006<sup>155</sup> review included the Collins<sup>160</sup> review, thereby including findings from Ortenstrand 2001<sup>110</sup> and Ortenstrand 1999.<sup>109</sup>

for infants' mean weight (g) at discharge (I:  $2381 \pm 315$ ; C:  $2460 \pm 317$ ;  $p = 0.05$ ) and number of days breastfeeding in hospital (I:  $2.5 \pm 2.0$ ; C:  $4.4 \pm 2.8$ ;  $p < 0.0001$ ).<sup>127</sup> These characteristics were significantly in favour of the control group.

Inclusion criteria for the Swedish trial specified that infants must be medically stable for more than 1 week, experience no apnoeic episodes and be able to maintain normal body temperature in an open crib.<sup>109,110</sup> Gavage feeding excluded infants in the control group from discharge.<sup>109</sup>

Mothers of infants in both trials were reported to have a mean maternal age of approximately 30 years<sup>127</sup> and 31 years<sup>109</sup> across both groups, and data from both trials indicate they were not significantly socioeconomically deprived. Over 90% of women in each group intended to breastfeed in the New Zealand trial.<sup>127</sup> Infant feeding intention was not reported in the Swedish trial although breastfeeding rates have been maintained at around 98% of all women in Sweden since 1991.<sup>167</sup>

### **Characteristics of interventions**

Both trials evaluated the effectiveness of early discharge with domiciliary nursing support compared with standard neonatal care.<sup>109,110,127</sup>

Infants receiving routine care in the New Zealand study unit were discharged when competent to feed orally by breast or bottle without cardiorespiratory compromise and they had a sustained pattern of weight gain after the establishment of full oral feeding and adequate maintenance of normal body temperature when fully clothed in an open cot.<sup>127</sup> Infants in the intervention group were discharged early with home support when meeting the same criteria but without the need for weight gain.<sup>127</sup>

In the Swedish trial,<sup>109</sup> discharge criteria did not include any weight limit for either group but all infants had to be clinically well and able to gain weight satisfactorily by breast or bottle feeding.

An individual care plan was developed in conjunction with a parent for participants in the intervention group in one study.<sup>109,110</sup> This included information on the care and safety of preterm infants and instructions on nasogastric tube feeding, including a strategy to bring gavage feeding to an end with professional confirmation. Domiciliary care was provided by the project nurse, specialised in paediatric and neonatal nursing, and with the support from the hospital-based neonatologist, nutritionist, social worker

and psychiatric team. Consulting visits to the neonatologist on the ward were scheduled for infants with bronchopulmonary dysplasia or heart disease. Domiciliary nursing care was provided until each infant met the ordinary criteria of the ward for hospital discharge.

Home support for infants discharged early in the New Zealand trial<sup>127</sup> comprised daily visits for the first 7–10 days, including weekends, by a team of visiting nurse specialists who were also available by telephone 24 hours a day. Routine care comprised contact of each family by a team of experienced home care nurses to enable visiting to occur in hospital and after discharge. The home care nurses made home visits or telephone contact during office hours on weekdays on a daily basis for the first five weekdays after discharge and thereafter depending on support required.

### **Outcome assessment**

Both trials reported the duration of any and exclusive breastfeeding at various time points. One trial reported duration rates at discharge and 6 weeks and 6 months after discharge<sup>127</sup> and one trial reported duration rates after completion of the domiciliary care programme and at 6 months.<sup>109,110</sup> This trial also reported the total duration of the lactation period.

Weight gain was reported in one trial as mean weight (g) 6 weeks after discharge and weight gain (g/kg) per day.<sup>127</sup> Both trials reported rates of readmission to hospital including at 6 weeks after discharge and 6 months of age<sup>127</sup> and during the first year follow-up period.<sup>109</sup>

Psychosocial outcomes were the primary focus of the Swedish trial,<sup>109,110</sup> including parental anxiety at hospital discharge, on completion of the domiciliary care programme and at 1 year, and parental assessment of their infant's health at 1 year. Parental satisfaction with duration of breastfeeding was also reported.<sup>109,110</sup> Examples of positive and adverse comments by parents participating in the New Zealand trial were reported.<sup>127</sup>

Both trials reported a range of process outcomes potentially influencing the effectiveness of the intervention<sup>109,127</sup> with one trial reporting numbers of home visits achieved according to the individual care plan.<sup>110</sup>

Cost-effectiveness outcomes were not reported in either trial.<sup>109,110,127</sup>

### Methodological quality of included trials

One RCT<sup>127</sup> was rated as moderate quality. This relatively large trial reported detailed participant characteristics at baseline and process outcomes to further interpret comparability of groups before and during the intervention.<sup>127</sup> Significant differences in some infant characteristics at baseline, however, warrant caution in interpretation of findings (see below for details). This trial conducted appropriate statistical analyses but failed to present supporting numerator, denominator or percentage data for comparison groups. Failure to report withdrawals further limits scope to assess whether analysis has been conducted on an ITT basis.<sup>127</sup>

One RCT<sup>109,110</sup> was rated as poor quality. This trial presented breastfeeding outcome data as an illustrative graph without supporting numerator, denominator or percentage data.<sup>109,110</sup> Primary outcomes of interest for this trial were reported appropriately, however, and using an ITT analysis. Inadequate methods of randomisation and concealment, the absence of an a priori sample size calculation, and the moderate size of the trial warrant caution in interpretation of findings reported in this trial.<sup>109,110</sup>

Details of the quality ratings for both trials are provided in *Table 86* in Appendix 5.

### Effectiveness of interventions

#### Primary outcomes

Results are not presented in a forest plot due to lack of appropriate outcome data in both trials and the poor quality rating of one RCT.<sup>109,110</sup>

Neither trial found statistically significant differences in duration rates of any or exclusive breastfeeding at various time points up to 6 months after discharge<sup>127</sup> or 6 months (definition not specified).<sup>110</sup>

#### Secondary outcomes

A significantly lower mean infant weight (g) was reported among the intervention group than the control group at 6 weeks after discharge (I: 4034 ± 592; C: 4189 ± 731;  $p < 0.04$ ) in one trial.<sup>127</sup> Daily weight gain (g/kg) measured for an undefined period was comparable (I: 12.18 ± 2.98; C: 12.15 ± 3.61; NS).<sup>127</sup>

The authors of one trial<sup>127</sup> reported no significant effect on rates of readmission to hospital at 6 weeks ( $p = 0.37$ ) after discharge or at 6 months of age ( $p = 0.96$ ). This was consistent with findings from

the other trial,<sup>109</sup> which reported no statistically significant differences between the groups in terms of rehospitalisations during the first year after discharge ( $p = 1.0$ ).

A significant reduction in hospital stay of infants in the intervention group was reported as a result of the intervention in both trials.<sup>109,110,127</sup> One trial reported a mean hospital stay that was 9.3 days shorter<sup>109,110</sup> and one reported a reduction to 2.5 days in the intervention group compared with 4.4 days in the control group.<sup>127</sup>

Personality trait anxiety scores (mean scores) among mothers in the early discharge group were not increased compared with the control group at discharge [I: 32.8 (SD 5.9); C: 33.3 (SD 7.9),  $p = 0.75$ ] and on completion of their domiciliary care programme [I: 31.7 (SD 7.1); C: 31.1 (SD 7.8),  $p = 0.74$ ].<sup>109,110</sup> Mean personality trait anxiety scores of fathers were lower in the intervention than in the control group at discharge [I: 27.8 (SD 5.9); C: 33.5 (SD 7.7),  $p < 0.05$ ] and on completion of the domiciliary care programme [I: 29.0 (SD 6.1); C: 32.3 (6.9),  $p < 0.05$ ]. Anxiety levels and confidence in handling the infant were comparable between groups at 1 year for both mothers and fathers.<sup>109,110</sup> This same trial reported lower levels of maternal satisfaction with the duration of breastfeeding among the intervention than the control group (I: 59.5%; C: 72.7%;  $X^2(1) = 0.8$ ;  $p = 0.36$ ).<sup>109,110</sup>

### Results from other study designs

No studies other than those included in systematic reviews or RCTs were identified.

### Organisation of care interventions

No studies were identified that evaluated changes to organisation of care between units, for example, introduction of a clinical network. A total of four primary studies<sup>137,138,151,154</sup> evaluating organisation of intra-unit care interventions were identified. As detailed in *Table 14*, one systematic review (McInnes and Chambers 2006)<sup>161</sup> included two of these primary studies<sup>138,143</sup> although one was assessed in that review as a study of finger feeding<sup>138</sup> and not organisation of care. Three<sup>137,138,152</sup> of the four primary studies were conducted in industrialised country settings and one was conducted in Brazil.<sup>151</sup> No RCTs or concurrent comparisons evaluating organisation of care were identified.

## Results from RCTs

No RCTs evaluating organisation of care were identified.

## Results from other forms of controlled studies

Four before/after studies evaluating organisation of care compared with previous standard care were identified<sup>137,138,151,154</sup> (see *Tables 70–72* in Appendix 4.1).

### Characteristics of participants

Two studies included all surviving infants with medical records who had been born at the study hospital and admitted to the neonatal care unit during the defined study periods.<sup>137,151</sup>

In one of these studies,<sup>137</sup> only 44% (117/264) of all infants in the unit met the inclusion criteria. Most were excluded on unspecified grounds; other reasons included medical records, lack of feeding data, ineligibility to breastfeed, adoption or custody issues.

Mothers in this study<sup>137</sup> were mostly black American or Hispanic and over half were on low incomes based on receipt of Medicaid. Nearly two-thirds of included infants were preterm with a gestational age of 30–37 weeks (B: 51.8%; A: 61.5%) or < 30 weeks (B: 4.5%; A: 6%). The remaining infants had a gestational age of > 37 weeks. Mean birthweight (g) for all infants was 2619 (SD 987) for the before group and 2506 (SD 939) for the after group; details by gestational age or proportions across the range were not reported. All infants were receiving enteral feeds by 2 weeks of age. Breastfeeding initiation rates for black American women are typically lower (52%) than the general population (69%) based on 2001 data.<sup>168</sup> Baseline rates would

be expected to be lower among mothers of infants in neonatal care.

The second study<sup>151</sup> excluded one mother who had no desire to breastfeed although this was not specified as an inclusion criterion for this study. This may reflect the typically high breastfeeding rates experienced in Brazil – 92% of infants were reported as having been ever breastfed in 1996; thus it is very unlikely that a mother would express no desire to breastfeed [WHO Global Data Bank on Breastfeeding and Complementary Feeding (<http://apps.who.int/research/iycf/bfcf/bfcf.asp?menu=11>), accessed 20 December 2007].

The study did not report participant characteristics by group or comparability at baseline.<sup>151</sup> Nearly 80% of all included infants were preterm and nearly 80% had a birthweight of < 2500 g. Although this study took place in the high-risk ward, no details were provided on the proportions of infants with very low birthweight. Only 13% of all included infants were classified as small for gestational age and 77% of all infants were on enteral feeds.<sup>151</sup> Mothers' mean age was 25 years (SD 6.7) with approximately 50% of mothers having < 4 or 5–12 years of education.

Another US study included only mothers of infants in the study unit who intended to breastfeed.<sup>154</sup> The study conducted in Australia included infants born at the study hospital at 34–35 weeks' gestation.<sup>138</sup> No participants' characteristics, comparability at baseline, numbers excluded and reasons for exclusions were reported for either study.

### Characteristics of interventions

Three studies evaluated the effect of Baby Friendly accreditation for the maternity hospital on neonatal care, comparing this with standard care

**TABLE 14** Included studies for 'organisation of care interventions'

Primary paper	Study design (n analysed) <sup>a</sup>	Inclusion in a systematic review	Country
Bicalho-Mancini 2004 <sup>151</sup>	Before/after (n = 495)	No	Brazil
Bell 1995 <sup>154</sup>	Before/after (n = 117)	No	USA
Merewood 2003 <sup>137</sup>	Before/after (n = 227)	Mclnnes 2006 <sup>161</sup>	USA
Oddy 2003 <sup>138</sup>	Before/after (n = 35)	<sup>b</sup> Mclnnes 2006 <sup>161</sup>	Australia

a The 'number analysed' refers to the numbers used by the review authors where it was possible to adjust for legitimate post randomisation exclusions. If this was not possible, the 'number analysed' refers to the numbers of participants for whom data were available for analysis as reported by study authors.

b Assessed by Mclnnes 2006 as an intervention of finger feeding, not organisation of care.

previously provided.<sup>137,138,151</sup> The remaining study<sup>154</sup> was a multifaceted intervention that evaluated the effect of protocol-based care for breastfeeding for the preterm or ill infant combined with assessment of staff educational needs and patient/family teaching records.<sup>154</sup>

Specific changes to practice following Baby Friendly accreditation were detailed in one study.<sup>138</sup> These included the need for a signed consent form for mothers if they requested a bottle feed or pacifier for their infant, maternal education, ongoing staff education, and a home visiting scheme. 'Finger feeding', which is feeding via a nasogastric tube attached to the carer's finger in place of a bottle and teat, was also introduced as a result of a different staff training event at the same time. Standard care for introduction of suck feeds prior to Baby Friendly accreditation was either breast or bottle feeds.<sup>138</sup>

The protocol-based care intervention was developed as standard for the paediatric nursing division, as guidelines for orientation of residents and staff physicians and as an educational tool and guide for parents.<sup>154</sup> It included initial education of mothers through written materials and a video supported by nurses facilitating initiation of pumping within 24 hours of birth. All mothers were provided with a kit for double pumping. The second stage of the protocol recommended use of skin-to-skin or kangaroo care for initiating non-nutritive time at the breast. Recognition of appropriate hunger cues and latching technique combined with use of the Systematic Assessment of the Infant at the Breast (SAIB) scale were recommended to assess appropriate progress through the transitional stages of non-nutritive and nutritive sucking and breastfeeding. Continued pumping and gavage feeding was advised until breastfeeding was established with no introduction of bottles until gavage supplements were not needed. The nurse should complete discharge teaching of breastfeeding and arrange for local breastfeeding support in the final stages.<sup>154</sup> Staff educational needs for implementation of the protocol were assessed followed by a programme of training by two certified lactation consultants. Staff received a resource manual and a pocket reference card for the SAIB scale. The final component of the intervention comprised a revised patient/family teaching record to include the protocol-based stages of breastfeeding.

### **Outcome assessment**

One study reported the initiation of breastfeeding and/or receiving breastmilk by any means during the first week of enteral feeds.<sup>137</sup> This study also reported duration of any, most or exclusive breastfeeding at 2 and 6 weeks.<sup>137</sup>

Two studies reported the duration of exclusive breastfeeding at hospital discharge<sup>138,151</sup> and one study reported duration of any breastfeeding at discharge.<sup>154</sup>

One study undertook multivariate logistic regression to assess independent risk factors associated with non-exclusive breastfeeding at discharge.<sup>151</sup>

No secondary outcomes were reported in any studies.

### **Methodological quality of included trials**

One study was rated as good quality.<sup>137</sup> It is worth noting, however, that study findings relate to 44% (117/264) of infants admitted to the unit; for details see Characteristics of participants (above); see also Chapter 7).

One study was rated as moderate quality.<sup>151</sup> This study was fairly large comprising a total of 495 participants across the before and after groups. Some caution is warranted in interpretation of findings from this study as the extensive list of characteristics of participants was not reported by group. Numerator and denominator data were not clearly reported for the primary outcome despite being detailed elsewhere in the paper.

The remaining two studies were rated as poor quality.<sup>138,154</sup> In addition, these studies had very small sample sizes in at least one of the comparison groups, and in Oddy and Glenn<sup>138</sup> the intervention coincided with a clinical intervention, the use of 'finger feeding'. Findings of these studies should be interpreted with serious caution.

All studies analysed complete data sets for participants according to their original comparison group. Losses post allocation do not apply for these studies where retrospective case-review methodology was applied according to defined inclusion criteria. Details of the quality ratings for both trials are provided in *Table 87* in Appendix 5.

### Effectiveness of interventions

#### Primary outcomes

Individual relative risk estimates have been calculated on an ITT basis for all four studies where relevant outcome data were reported.<sup>137,138,151,154</sup> These results are presented in forest plots for primary outcomes in the two studies that did not receive a poor overall quality rating.<sup>137,151</sup>

However, some caution is required in interpreting the results even of the better quality studies due to the inherent methodological weaknesses of a before/after study design. However, before/after studies are considered an appropriate study design for evaluations of a unit-wide multifaceted

organisation of care intervention such as the Baby Friendly Initiative (BFI).

One study<sup>137</sup> reported a significant increase in the number of infants receiving any breastmilk (by any means) during the first week of enteral feeds as a result of changes to organisation of care to achieve BFI accreditation ( $p = 0.00001$ ) (Figure 29).

This US study also reported significant between-group increases ( $p = 0.005$ ) in the duration of exclusive breastfeeding prior to discharge (at 2 weeks) after implementation of BFI accreditation<sup>137</sup> (Figure 30). Significant increases in rates of exclusive breastfeeding were also demonstrated at hospital discharge in a large ( $n = 495$ )

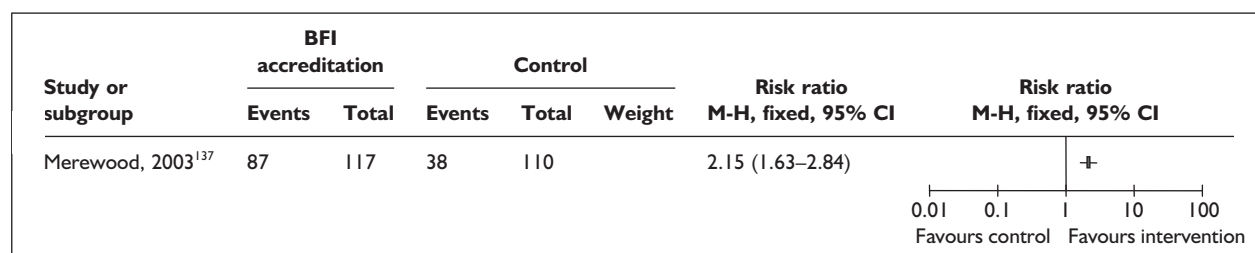


FIGURE 29 Baby Friendly accreditation vs previous care: any breastmilk during first week of enteral feeds (ITT).

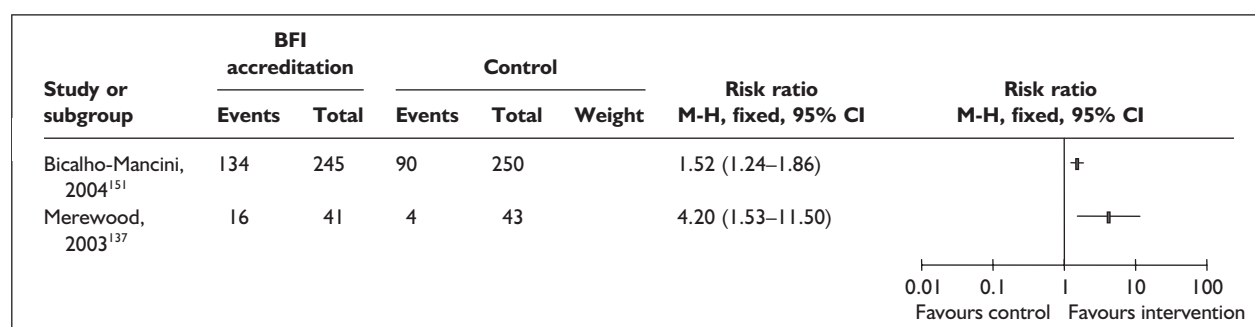


FIGURE 30 Baby Friendly accreditation vs previous care: exclusive breastfeeding at or prior to hospital discharge (ITT).

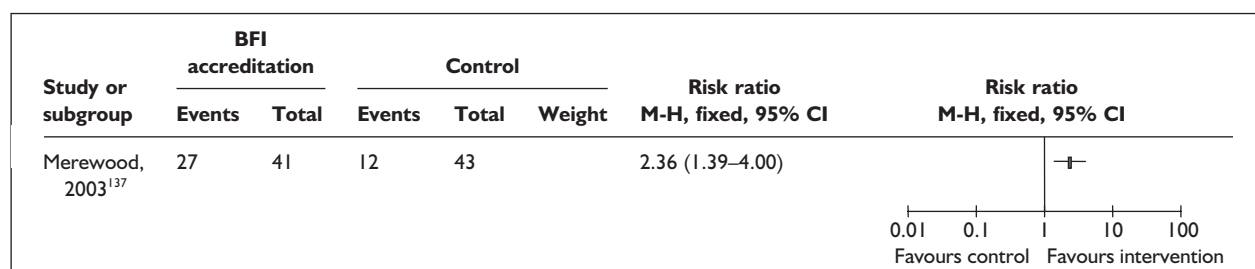


FIGURE 31 Baby Friendly accreditation vs previous care: any breastfeeding prior to hospital discharge (ITT).

moderate quality before/after evaluation of BFI accreditation.<sup>151</sup>

The US-based study<sup>137</sup> found a statistically significant increase in the duration of any breastfeeding prior to discharge (at 2 weeks) ( $p = 0.001$ ) among infants in neonatal intensive care (*Figure 31*). Numbers of infants remaining in the neonatal intensive care unit at 6 weeks were

too small to provide meaningful results for the duration of any breastfeeding at this time point (B: 1/8; A: 6/9).<sup>137</sup>

Neither of the two poor-quality studies identified differences in any or exclusive breastfeeding at hospital discharge or the percentage of women breastfeeding at discharge.<sup>138,154</sup> These findings warrant caution due to the study quality.





## Chapter 5

# Methods and results of economic modelling

### Modelling background

Economic evaluations play a vital role in the allocation of health-care resources, and help to inform decisions about the efficient allocation of those resources.<sup>169</sup> The use of decision analysis allows the incorporation of all relevant evidence into a single framework. This evidence can be derived from a variety of sources including meta-analyses, clinical trials and national databases. The complexities of the issues being addressed through modelling mean that the evidence on the consequences and costs of interventions often cannot be derived from a single source.

Decision models provide an *explicit* framework for the *implicit* decisions that are already being made.<sup>170</sup> The issues regarding the treatment and care of preterm infants are extremely complex. The question of how to promote breastfeeding efficiently in neonatal units cannot easily be answered, and is certainly not answerable with reference to a single study. The use of an analytical framework, that is to say, a decision model, to allow the synthesis of all available evidence will provide decision-makers with a clearer picture of the meaning of the available evidence and where the uncertainty lies, and will assist in identifying crucial gaps in the available evidence.

The evidence base relating to breastfeeding in this particular population is scant, particularly in the area of economics. This is borne out by the lack of economic evaluations identified for inclusion within the review. However, it is important that all the available evidence is used to establish the long-term costs and benefits of increasing the uptake of breastfeeding in this population. Given the sparse nature of the evidence base the model used is likely to be an oversimplification of a complex problem. However, capturing all of the available evidence in a single framework will provide us with some useful evidence, while also generating some important and relevant questions and offering potential for use in future research.

### Methods for health economics modelling

This work was informed throughout by input from clinical experts (see Appendix 1 and Acknowledgements) and by discussion within the whole research team. In the absence of any existing economic evidence, the decision was made to develop a decision model for one important topic, enhanced staff contact. This included both additional skilled support from staff and staff training. These interventions are discussed in the previous chapter (see Breastfeeding education and support interventions; and Staff training interventions). Only one study of support<sup>166</sup> and one of staff training<sup>149</sup> included all mothers, not just those intending to breastfeed, and therefore these studies were used to inform the concept of 'enhanced staff contact'.

While other approaches to the promotion of breastfeeding were considered in the main effectiveness review, the issue of enhanced staff contact was deemed the most useful and applicable decision problem to evaluate in this part of the work. It was noted that the effectiveness of enhanced staff contact will also depend on the milk expression methods and incentives available in any particular centre, and the attraction of breastfeeding to the mother is likely to depend on privacy and ease of expression, storage and delivery of milk to the neonatal unit. Therefore, this model investigates the cost-effectiveness of enhanced staff contact given reasonable provision of privacy arrangements and free expression kits.

A decision tree was developed, using the software package DATA PROFESSIONAL (TreeAge Software) to synthesise data on enhanced staff contact, breastmilk effectiveness, incidence of necrotising enterocolitis (NEC) and sepsis, resource use, survival and utilities. The objective of the model was to estimate the long-term costs and benefits of enhanced staff contact in promoting breastfeeding

to mothers whose infants were admitted to neonatal units.

The premise of the model structure was that enhanced staff contact increases milk expression; in turn, it was assumed that this would lead to increased milk consumption by the infant. Milk consumption was then assumed to reduce the incidence of illness episodes thereby improving long-term health outcomes. The health benefits evaluated were quality-adjusted life-years (QALYs).

The population of interest was defined in accordance with the inclusion criteria for the review, that is to say, all mothers with infants in neonatal units. However, the evidence suggested that the greatest benefit could be achieved in those infants born earlier and smaller, therefore the population was limited to those infants < 2500 g. For the purpose of model development a hypothetical cohort of indeterminate size was divided into weight-based subgroups, which were modelled separately. The clinical rationale for these subgroups was that the incidence of diseases increases greatly as the birthweight decreases. These subgroups were: 500–999 g; 1000–1749 g; and 1750–2500 g. The perspective was that of the NHS, and costs and benefits were discounted at an annual rate of 3.5%, as recommended by the current NICE guidelines.<sup>103</sup>

The structure of the model was determined by the evidence obtained during early stages of the effectiveness review, and by clinical studies identified in the additional modelling searches (see Appendix 2.3). It was then finalised by means of a series of meetings with clinical advisors. An illustration of the model structure is provided in Figures 32–34. A brief summary of the structure is provided in the following section; a number of subheadings have been used to aid understanding. A number of assumptions were made to facilitate

modelling; these are outlined and explained in a later section.

### Interventions

The two interventions evaluated in the base-case model were enhanced staff contact – the addition of specially trained staff, who would be available to advise and support mothers on milk expression and breastfeeding, compared with normal staff contact – that is to say, no addition of specially trained staff.

### Intention to breastfeed

The model starts by dividing the population into those women who intend to breastfeed and those who do not intend to breastfeed prior to their infant’s birth. The literature suggested that the mother’s intention influenced the infant’s likely breastmilk consumption level<sup>171</sup> (Figure 32).

### Breastmilk effectiveness

The model was designed to capture the health effects for three different levels of milk consumption, namely:

- all own mother’s milk
- some mothers’ milk, which was supplemented by formula in the base case
- formula alone.

The literature suggested that different levels of mothers’ milk consumption impacted on the health of the infant. In addition, the literature demonstrated that there were differences in effectiveness between donor breastmilk and preterm formula and, therefore, potential cost and benefit differences.

Currently in the UK donor breastmilk is neither widely nor readily available in the majority of units. In order to reflect this, two separate models were used in an attempt to capture the current

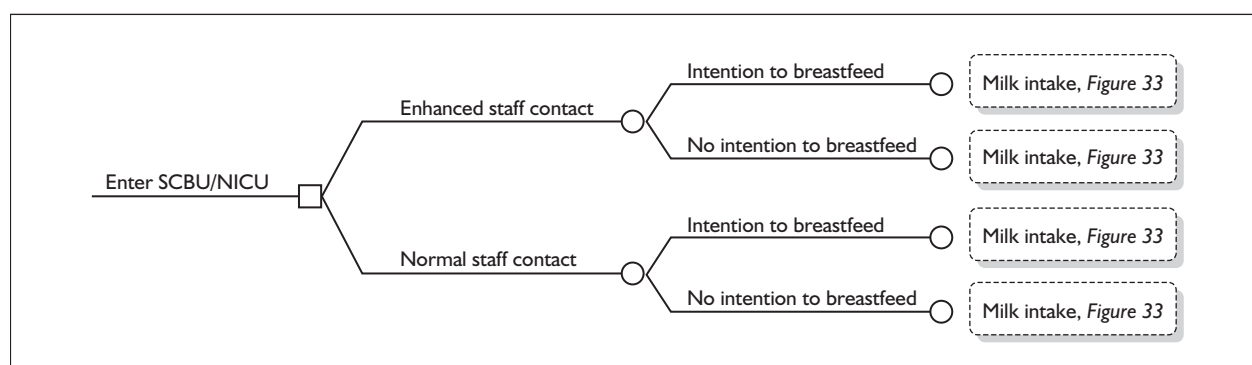


FIGURE 32 Model structure: intention to breastfeed.

situation where the use of donor breastmilk would be dictated by availability not choice. So, with the limited number of donor milk banks, the majority of infants would receive preterm formula due to a lack of any other option. By using two separate models, we hoped that we would be able to provide useful information regarding the long-term costs and benefits of supplementing with donor milk, alongside the long-term costs and benefits of supplementing with preterm formula, thereby reflecting the two separate situations that are current practice in the UK.

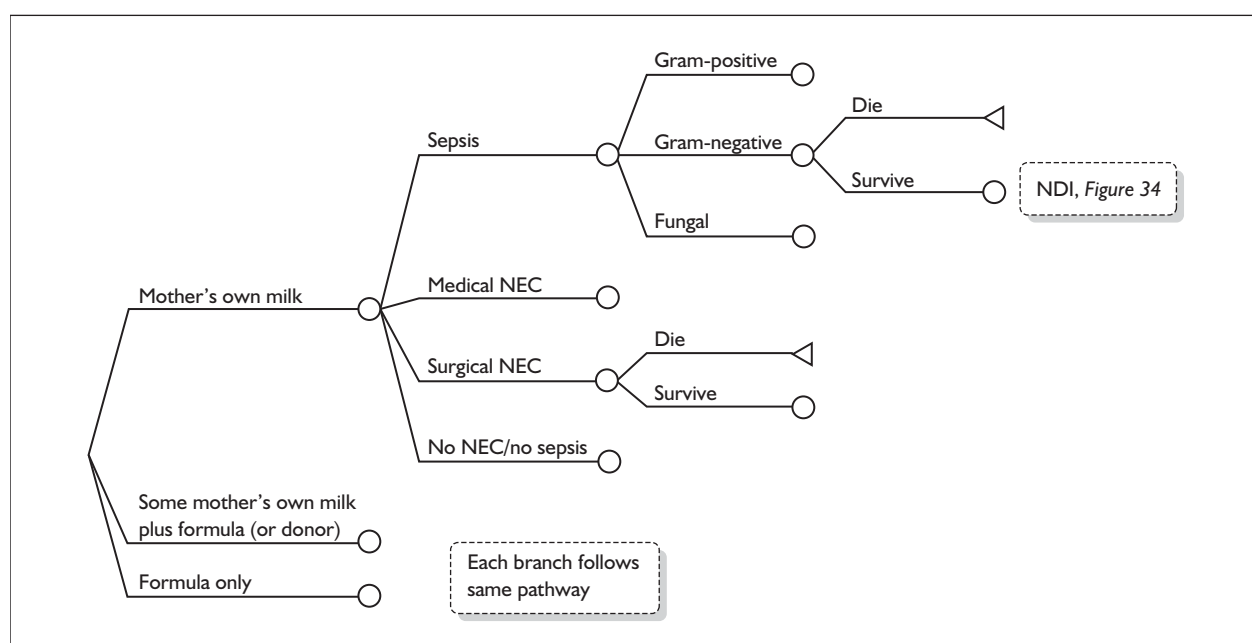
### Clinical outcomes

The in-hospital clinical outcomes of interest were sepsis, confirmed NEC (Bell stage II or greater) and mortality. These clinical outcomes, while not an exhaustive list, were deemed by our clinical advisors to be the most common and clinically relevant outcomes that are claimed to be linked to breastmilk intake. NEC was divided into medically treated NEC and surgically treated NEC, as both outcomes and resources varied depending on treatment. Suspected NEC was excluded from the analysis. As health benefits and potential resource use also varied dependent on the type of sepsis, this was subdivided into Gram-negative, Gram-positive and fungal infection. Mortality rates varied depending on the diagnosis (see *Table 15*). These subdivisions of clinical outcomes allowed the differences in resource use and utility outcomes to be captured (*Figure 33*).

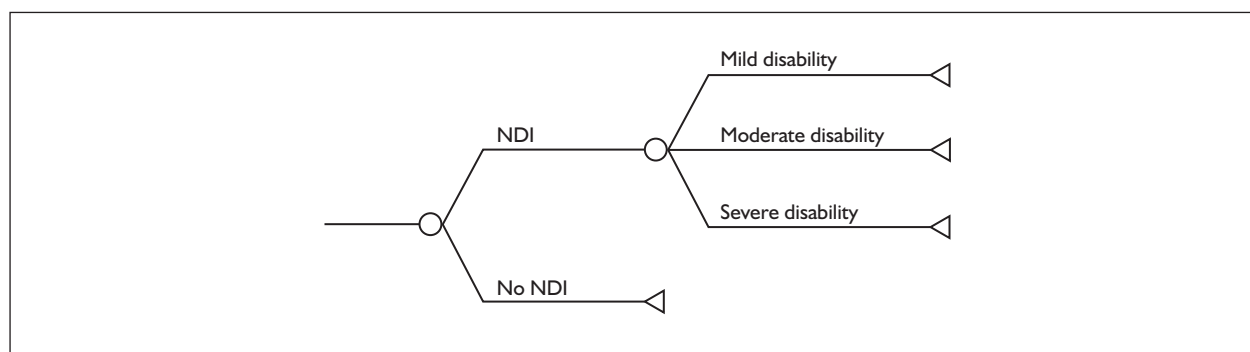
## Long-term outcomes

The selected clinical outcomes are considered to be intermediate outcomes and it was therefore necessary to link these to a final outcome.

In this instance, QALYs were used as the long-term outcome. This was achieved by a two-step process. First, the intermediate outcomes were linked to disability by means of neurodevelopmental impairment (NDI), which was reported in the clinical papers identified. NDI is a composite measure that captures many elements of disability including visual impairment, hearing impairment and mobility. The NDI scores were divided into four disability categories, namely: no disability, mild disability, moderate disability and severe disability. The probability of the infant ending up in each state depended on their clinical pathway. Utility values for each of the health states were then used to quality-weight life expectancy. Utilities are used as a means of representing the strength of individuals' preferences for precise outcomes, in this instance disability states, under conditions of uncertainty. They fall between 0 and 1, with 1 representing perfect health. Life expectancy for infants in each of the four disability states was taken from Colbourn *et al.* (2007).<sup>172</sup> A combination of life expectancy and utilities were used to derive QALYs for each of the disability states. These were discounted at an annual rate of 3.5% (*Figure 34*). Discounting is a widely accepted practice in



**FIGURE 33** Model structure: breastmilk effectiveness and intermediate health outcomes. NEC, necrotising enterocolitis.



**FIGURE 34** Model structure: long-term outcomes. NDI, neurodevelopmental impairment

economic evaluations and allows future gains and losses to be weighted to reflect preferences for consumption now rather than in the future.<sup>103</sup>

## Modelling assumptions

In order to facilitate modelling a number of simplifying assumptions were required. These are outlined below.

1. It was assumed that clinical data from a number of countries, mainly the USA, were transferable to the UK setting.
2. The impact of fortification of mothers' milk was assumed to be neutral. It can be assumed that all breastmilk data from the USA are based on fortified milk. However, this is not the case in the UK, where fortification is not routine practice. Data were derived from studies conducted in both settings.
3. In the base case, the effectiveness of enhanced staff contact was assumed to be equal regardless of the intent of the mother regarding breastfeeding. This assumption was tested in sensitivity analysis. (Details of the findings are presented below; see Intervention effectiveness estimate.)
4. The disability health state of the infant at diagnosis was assumed to remain constant throughout the lifetime of the infant. This may seem like a strong assumption; however, there was no evidence to suggest that an infant diagnosed as moderately disabled would either improve enough to change their classification to mild, or deteriorate sufficiently to change their classification to severe. Therefore, no sensitivity analysis was undertaken.
5. The issues of multiple births have not been considered.
6. The main possible health effects specific to this population of feeding mothers' breastmilk

to infants in neonatal units are on the reduction of NEC and sepsis. The negative effect of breastmilk through postnatal vertical transmission of cytomegalovirus has not been incorporated into the model. Other outcomes such as gastroenteritis, respiratory disease, and cognitive impairment have not been considered.

The search process to support the economic model was undertaken in a number of stages and included those searches already undertaken for the systematic review of economic evaluations (see Chapter 3). Full details of all searches relevant to the economics are presented in Appendix 2.2.

## Input parameters

All model input parameters are presented in *Table 15*.

### Interventions

The intervention evaluated was enhanced staff contact, which consisted of additional specially trained staff. Two papers were considered appropriate for inclusion: Gonzalez *et al.* (2003)<sup>166</sup> and Pineda (2006),<sup>149</sup> which both included a suitable intervention, aimed at all mothers with infants in a neonatal unit. These two papers provided us with the probability of an infant receiving his or her own mother's milk. Gonzalez *et al.*<sup>166</sup> evaluated the introduction of a lactation consultant, and Pineda<sup>149</sup> the introduction of staff education and leaflets. For the purpose of the base case, we have assumed that both interventions lead to the same amount of enhanced specially trained staff contact for the mothers and infants. Therefore, a pooled odds ratio weighted by sample size was derived. This was then translated into a probability, which was used in the model. This assumption was tested in sensitivity analysis.

TABLE 15 Model data inputs

Data	Mean or odds ratio	SD or 95% CI	Source
Intention to breastfeed rate	0.72		Bolling 2007 <sup>49</sup>
<b>For the enhanced staff contact intervention</b>			
<i>For mothers intending to breastfeed</i>			
Probability of MM > 80% of total milk intake	0.678		ˆSisk 2006 <sup>106</sup>
Probability of 80% > MM > 0.01% of total milk intake	0.278		ˆSisk 2006 <sup>106</sup>
Probability of MM < 0.01% of total milk intake	0.043		ˆSisk 2006 <sup>106</sup>
<i>For mothers not intending to breastfeed</i>			
Probability of MM > 80% of total milk intake	0.160		ˆSisk 2006 <sup>106</sup>
Probability of 80% > MM > 0.01% of total milk intake	0.506		ˆSisk 2006 <sup>106</sup>
Probability of MM < 0.01% of total milk intake	0.333		ˆSisk 2006 <sup>106</sup>
<b>For the normal staff contact intervention</b>			
Odds of ever receiving own mother's milk			
Normal staff contact vs enhanced contact	0.500	0.34–0.75	Gonzalez 2003, <sup>166</sup> Pineda 2006 <sup>149</sup>
<b>Baseline incidences given MM and formula consumption</b>			
<i>Incidence of sepsis by weight subgroup</i>			
500–999 g	0.272		Fanaroff 1998 <sup>177</sup>
1000–1749 g	0.082		Fanaroff 1998 <sup>177</sup>
1750–2500 g	0.047		Fanaroff 1998 <sup>177</sup>
<i>Incidence of medical NEC by weight subgroup</i>			
500–999 g	0.035		Guthrie 2003 <sup>176</sup>
1000–1749 g	0.021		Guthrie 2003 <sup>176</sup>
1750–2500 g	0.005		Guthrie 2003 <sup>176</sup>
<i>Incidence of surgical NEC by weight subgroup</i>			
500–999 g	0.033		Guthrie 2003 <sup>176</sup>
1000–1749 g	0.006		Guthrie 2003 <sup>176</sup>
1750–2500 g	0.001		Guthrie 2003 <sup>176</sup>
<i>Odds of confirmed NEC (medical and surgical)</i>			
MM vs MM and donor <sup>a</sup>	0.885	0.69	Schanler 2005 <sup>173</sup>
MM and donor vs MM and formula <sup>b</sup>	0.465	0.656	Lucas 1990 <sup>174</sup>
Formula vs MM and formula	3.006	0.40	Lucas 1990 <sup>174</sup>
<i>Odds of sepsis</i>			
MM vs MM and donor	0.709	0.38	Schanler 2005 <sup>173</sup>
MM and donor vs MM and formula	0.997	0.34	Schanler 2005 <sup>173</sup>
Formula vs MM and formula	0.803	0.15	Vohr 2006 <sup>10</sup>
<i>Distribution of sepsis cultures</i>			
Gram-positive	0.689		Stoll 2002 <sup>178</sup>
Gram-negative	0.196		Stoll 2002 <sup>178</sup>
Fungal	0.115		Stoll 2002 <sup>178</sup>

continued

TABLE 15 Model data inputs (continued)

Data	Mean or odds ratio	SD or 95% CI	Source
<i>Baseline mortality rates given no disease</i>			
500–999 g	0.205		Hintz 2005 <sup>179</sup>
1000–1749 g	0.08		Fanaroff 1998, <sup>177</sup> Stoll 2002 <sup>178</sup>
1750–2500 g	0.05		<sup>d</sup> NHS, Scotland
<i>Odds of mortality</i>			
Gram-positive sepsis vs no disease	1.609	0.12	Stoll 2002 <sup>178</sup>
Gram-negative sepsis vs no disease	7.263	0.14	Stoll 2002 <sup>178</sup>
Fungal sepsis vs no disease	5.969	0.18	Stoll 2002 <sup>178</sup>
Medical NEC vs no disease	2.055	0.14	Hintz 2005 <sup>179</sup>
Surgical NEC vs no disease	3.124	0.12	Hintz 2005 <sup>179</sup>
<i>Baseline incidence of NDI given no disease</i>			
500–999 g	0.485		Larroque 2008 <sup>180</sup>
1000–1749 g	0.413		Larroque 2008 <sup>180</sup>
1750–2500 g	0.343		Larroque 2008 <sup>180</sup>
<i>Odds of NDI</i>			
Sepsis vs no disease	2.282	0.07	Stoll 2004 <sup>181</sup>
Medical NEC vs no disease	1.187	0.19	Hintz 2005 <sup>179</sup>
Surgical NEC vs no disease	1.985	0.19	Hintz 2005 <sup>179</sup>
<b><i>Distribution of severity of disability given NDI</i></b>			
<i>Severe disability</i>			
500–999 g	0.164		Larroque 2008 <sup>180</sup>
1000–1749 g	0.079		Larroque 2008 <sup>180</sup>
1750–2500 g	0.141		Larroque 2008 <sup>180</sup>
<i>Moderate disability</i>			
500–999 g	0.297		Larroque 2008 <sup>180</sup>
1000–1749 g	0.236		Larroque 2008 <sup>180</sup>
1750–2500 g	0.209		Larroque 2008 <sup>180</sup>
<i>Mild disability</i>			
500–999 g	0.538		Larroque 2008 <sup>180</sup>
1000–1749 g	0.685		Larroque 2008 <sup>180</sup>
1750–2500 g	0.650		Larroque 2008 <sup>180</sup>
<i>Utilities</i>			
No disability	0.940	0.12	Colbourn 2007 <sup>172</sup>
Mild disability	0.850	0.10	Colbourn 2007 <sup>172</sup>
Moderate disability	0.645	0.12	Colbourn 2007 <sup>172</sup>
Severe disability	0.470	0.25	Colbourn 2007 <sup>172</sup>

TABLE 15 Model data inputs

Data	Mean or odds ratio	SD or 95% CI	Source
<i>Life expectancy</i>			
No disability	78.5		Colbourn 2007 <sup>172</sup>
Mild disability	78.5		Colbourn 2007 <sup>172</sup>
Moderate disability	67.8		Colbourn 2007 <sup>172</sup>
Severe disability	26.1		Colbourn 2007 <sup>172</sup>
<b>Costs</b>			
<i>Minutes of staff contact time<sup>e</sup></i>			
Initial contact	45		Gonzalez 2003 <sup>166</sup>
Further contact	150		Gonzalez 2003 <sup>166</sup>
<i>Unit costs (£)</i>			
Registered nurse (£/hour)	41.12		Curtis 2006 <sup>183</sup>
Level 1 neonatal unit	939.00	310.20	DH 2008 <sup>184</sup>
Level 2 neonatal unit	671.00	178.38	DH 2008 <sup>184</sup>
Special Care Baby Unit	405.00	99.80	DH 2008 <sup>184</sup>
Major neonatal diagnosis	1514.00	838.10	DH 2008 <sup>184</sup>
<i>Lifetime cost of disability (£)</i>			
Mild disability	14,421		Colbourn 2007 <sup>172</sup>
Moderate disability	13,959		Colbourn 2007 <sup>172</sup>
Severe disability	364,005		Colbourn 2007 <sup>172</sup>

DH, Department of Health; MM, mothers' milk; NDI, neurodevelopmental impairment; NEC, necrotising enterocolitis.  
a Mothers' milk and donor milk supplements.  
b Mothers' milk and formula supplements.  
c Supplemented by personal communication from the author.  
d *Small Infants in Scotland*, Information and Statistics Division, NHS Scotland.  
e See Table 16 for length of stay data.

### Intention to breastfeed and intervention effectiveness

A baseline intention to breastfeed rate for England and Wales was taken from the Infant Feeding Survey 2005.<sup>49</sup> This rate was varied across plausible ranges, including the Northern Ireland rate, in sensitivity analysis.

Data from Sisk *et al.* (2006)<sup>106</sup> were used to estimate incidence rates for the different types of milk consumption (all own mother's milk, some own mother's milk and formula) for mothers who intended to breastfeed prior to birth and those who did not. As the Sisk paper<sup>106</sup> evaluated lactation counselling for mothers, the data obtained were used as the baseline for the enhanced staff contact branch of the model, as this seemed most appropriate.

The normal staff contact probabilities were obtained by adjusting the rate of receiving the different consumption levels by the relative effectiveness of the intervention.

### Breastmilk effectiveness

The literature was searched for papers that reported two or more of the milk consumption categories of interest, namely: (1) formula only; (2) some mothers' milk and formula supplement; (3) some mothers' milk and donor supplement; and (4) mostly or all own mother's milk (mostly was defined as > 80%) – and which evaluated the impact of breastmilk consumption on either the incidence of confirmed NEC (stage II or III) or sepsis. Priority was given to systematic reviews, RCTs and cohort studies. Studies with larger study populations were given greater weight.

The studies identified for NEC outcomes were Schanler *et al.* (2005)<sup>173</sup> and Lucas and Cole (1990).<sup>174</sup> From the data provided in these papers a number of odds ratios were derived comparing different milk consumptions. In addition, studies identified for sepsis outcomes were Schanler *et al.* (2005)<sup>173</sup> and Vohr *et al.* (2006).<sup>10</sup> Fortifier was added to mothers' milk in the Schanler study,

and in 75% of breastmilk feeds without parenteral nutrition in the Vohr study. It is not routine practice in the UK to add fortifier to mothers' milk, and the impact of fortifier on outcomes is not clear but has been assumed neutral in this analysis.

### **Incidence of NEC/sepsis**

A number of studies were identified through the additional modelling searches that reported the incidence of NEC and sepsis. In order to derive model inputs it was necessary to identify those studies that either reported the data for the relevant subpopulations or that would allow the data for the subpopulations to be calculated. The baseline incidence rates of NEC for the relevant weight bands were obtained by combining absolute numbers of NEC from Gilbert *et al.* (2003)<sup>175</sup> with incidence rates per 250-g bands from Guthrie *et al.* (2003).<sup>176</sup> Discrete exponential growth of NEC prevalence numbers by birthweight bands was assumed. These data were deemed an appropriate baseline for the own mother's milk plus formula branch. As the model subdivided NEC into medical and surgical, these were the incidence data that we extracted from Guthrie *et al.*<sup>176</sup>

The baseline incidence of sepsis was derived from Fanaroff *et al.* (1998)<sup>177</sup> and, like the Guthrie paper,<sup>176</sup> the infants in the study had consumed a mix of own mother's milk supplemented by formula. Hence, the incidence data derived seem most appropriate to the own mother's milk plus formula branch. Sepsis data were presented as an aggregate rate and not for each of our subdivisions – Gram-positive, Gram-negative and fungal. Due to the differences in mortality rate and disability outcome that occur given each type of infection, it was important to ensure that the incidence of sepsis was further subdivided. The data for incidence of Gram-positive, Gram-negative and fungal were derived from Stoll *et al.* (2002)<sup>178</sup> and were used to ascertain the probability of Gram-positive, Gram-negative and fungal, given a diagnosis of sepsis.

### **Mortality**

Mortality rates varied depending on the subpopulation being evaluated and the clinical outcome. Baseline rates for no NEC/no sepsis was derived from Hintz *et al.* (2005)<sup>179</sup> for the 500–999 g group, from Fanaroff *et al.* (1998)<sup>177</sup> and Stoll *et al.* (2002)<sup>178</sup> for the 1000–1749 g group, and from a report *Small Infants in Scotland* ([http://isd.scot.nhs.uk/isd/files/mat\\_bb\\_small\\_babies.pdf](http://isd.scot.nhs.uk/isd/files/mat_bb_small_babies.pdf)) from the Information and Statistics Division of NHS Scotland for the 1750–2500 g group. The odds ratio for mortality given medical NEC and surgical NEC was also derived from the Hintz *et al.*<sup>179</sup> paper

and adjusted, where necessary, by the baseline mortality rate. Again, the probability of death given sepsis (Gram-positive, Gram-negative and fungal) was obtained from Stoll *et al.*<sup>178</sup> and adjusted for the baseline mortality rate in order to derive the probability of death given the clinical infection present in the infant.

### **Disability and utilities**

Preterm infants who survive NEC and sepsis can be left with long-term disabilities. For the purpose of the model, we assumed that infants could have no neurodevelopmental problems, mild disability, moderate disability or severe disability. The NDI, a composite measure that captures many elements of disability including visual impairment, hearing impairment and mobility, was derived from Larroque *et al.* (2008).<sup>180</sup> This was the only paper identified that reported the relevant data for the three weight populations of interest and that provided sufficient data on the distribution of disabilities between the three severities, i.e. mild, moderate and severe. The incidence of severe disability for the 1750–2500 g infants appeared to be quite high, and this parameter was therefore considered in sensitivity analysis. The odds ratio for developing NDI from sepsis compared to no disease was obtained from Stoll *et al.* (2004).<sup>181</sup> The odds ratio for developing NDI from medical or surgical NEC compared to no disease was obtained from Hintz *et al.*<sup>179</sup>

A published HTA report<sup>171</sup> was used to obtain the utility estimates. As previously outlined, utilities allow life-years to be given health quality weights. The HTA report used a primary study, that by Oostenbrink *et al.* (2002),<sup>182</sup> which had evaluated utilities using the EQ-5D to derive a valuation for preterm infants. The paper presented vignettes to 28 paediatricians in the Netherlands for seven case descriptions. In line with the approach taken by Colbourn *et al.*,<sup>172</sup> utilities for mild, moderate and severe disabilities were derived from these seven case descriptions by grouping them into three clusters of severity and taking the average. Life expectancy given the final disability state of the infant was also taken from the HTA report.<sup>172</sup>

### **Costing**

The perspective adopted for the economic evaluation was that of the service provider (UK NHS). In accordance with this perspective, the costs included in the economic analysis were the direct costs incurred as a result of the interventions. These included: the intervention costs, treatment of NEC and sepsis, length of inpatient stay in



level I, II or III units and the lifetime cost of disability. The price year was 2006/2007 and all prices were appropriately inflated using the health component of the consumer price index. Although the intervention will potentially increase breast pump resource use and donor milk consumption, and decrease formula consumption, these costs were excluded as independent cost items in the base-case model because the current practice of provision of breast pumps is not clear and therefore difficult to cost. It did not seem appropriate to include formula and not breast pumps or expression kits in the model, so both were left for sensitivity analyses to explore. Breast pumps and formula costs are likely to be included in the inpatient stay costs as part of hotel costs; however, this does not capture the incremental effect of the intervention on these resources.

#### ***The intervention***

The clinical effectiveness papers used to derive the model inputs concerned the provision of a lactation consultant to encourage the mothers to express milk, and to advise and help the mothers in expressing milk and answering general questions.

Resource use is represented by the time made available to the mothers by the lactation consultant. Using the paper by Gonzalez *et al.*,<sup>166</sup> this was assumed to be:

- 45 minutes of initial contact with each mother to encourage milk expressing
- 30 minutes developing milk expression plan
- 60 minutes helping milk expression at two sessions
- 60 minutes responding to questions and providing additional help.

For the purpose of our model, all mothers were initially assumed to use the full 45 minutes of specially trained staff time. However, only those mothers who decided to try to express milk were assumed to consume the extra time of the specially trained staff. Therefore, only those following the own mother's milk pathway and the some mothers' milk plus supplement pathway were assigned costs for the additional 2.5 hours of contact. This was an assumption on our part, as the paper did not provide sufficient detail to ascertain exactly how much time each mother or each pathway consumed. However, it is unlikely that if a mother decided not to express milk in order to feed her infant that further time would be spent initiating expression and establishing a milk plan.

The unit cost was based on the hourly rate of a registered sick children's nurse, which was varied in sensitivity analysis to reflect the increase in cost if a midwife were used to provide the additional support.

#### ***Treatment of NEC and sepsis***

The diagnosis of medical NEC and sepsis can include tests such as: microbiological culture tests for blood and urine; chest X-rays; cerebrospinal fluid; radiography; retinal examination; echocardiography; and renal ultrasonography. Treatments may include the use of broad-spectrum antibiotics, often intravenously administered; bowel rest; and regular monitoring of C-reactive protein and platelet count. These resources were not individually included as outlined below.

#### ***The unit cost of an inpatient day***

All hospitalised infants incur per patient/day costs as do infants without NEC/sepsis. The unit cost for an inpatient day was taken from the NHS Reference Costs for 2006/07<sup>184</sup> for the following levels:

1. Neonatal Intensive Care Level 1 – unit cost of £939
2. Neonatal Intensive Care Level 2 – unit cost of £671
3. Special Care Baby Unit (Level 3) – unit cost of £405.

Supporting documents for the NHS Reference Costs indicate that the unit costs for these units include: hotel services, nursing, therapy services, medical staff, ward consumables, blood and blood products, drugs, diagnostics (e.g. pathology and radiology), and medical and surgical equipment [including specialist equipment, e.g. CPAP (continuous positive airway pressure) and NIPPV (non-invasive positive pressure ventilation) machines]. No theatre costs are included.

#### ***The unit cost for treatment and diagnostics***

Identification of the volume and type of resources consumed was problematic and, as a result, the unit cost of an inpatient day for the three levels was used to reflect the different volumes consumed, and therefore costs incurred, by the infants. This assumption seemed reasonable given that the costs for the treatments and diagnostics appear to be included in the unit cost for an inpatient day. Additionally, if their costs had been derived separately, it was not clear if this would lead to an element of double counting.

### **Surgery costs**

Hall and Pierro (2004)<sup>185</sup> suggest that there are three general approaches to surgery for NEC. These are: peritoneal drainage alone, peritoneal drainage followed by laparotomy (bowel resection, stoma formation, clip and drop); and laparotomy alone (bowel resection, stoma formation, clip and drop).

Correspondence with several clinical experts suggested that peritoneal drainage alone is rarely conducted in the UK setting. Therefore, it was agreed that the cost of laparotomy alone or with drainage would be included in the model. The same unit cost was used for both procedures, as it was assumed that drainage and laparotomy were both included in the average cost of treating a major neonatal diagnosis. The unit cost was derived from the NHS Reference Costs.<sup>186</sup>

### **Length of stay**

Average length of stay data for the UK setting were not available. In order to facilitate modelling, we combined length of stay data from Bisquera *et al.*,<sup>29</sup> Stoll *et al.*<sup>178</sup> and Fanaroff *et al.*,<sup>177</sup> all these containing US data. These data were then used to derive length of stay estimates for the different levels of care for infants divided into the three weight groups and infants divided into the following health episode groups: no NEC/sepsis; sepsis; confirmed medical NEC; and surgical NEC. This information was used to estimate the number of days that infants within a certain weight category, having had a particular health episode, would spend consuming the resources required from a level 1 NICU and from a level 2 NICU or a SCBU (level 3). The length of stay details are presented in *Table 16*. It should be noted that *Table 16* shows the *incremental* length of stay in a level 1 unit attributable to NEC and, hence, for the control group is zero. The unit cost for consuming resources from a level 2 NICU or a SCBU will be an average of the unit costs for the levels of care specified above.

### **Lifetime disability costs**

For each year of life it was necessary to include an annual cost that would be incurred solely as a result of the disability state. These costs were taken from Trotter and Edmunds (2002),<sup>187</sup> who identified costs for mild, moderate and severe disability given survival of meningococcal disease, which can result in a variety of long-term sequelae. The authors derived their estimates from the Unit Costs of Health and Social Care, 2000. These costs adjusted for inflation are presented in *Table 17*.

## **Cost-effectiveness analysis**

### **Incremental analysis**

To compare the costs and consequences of the alternative intervention strategies, cost-effectiveness ratios were estimated as the cost per QALY gained. Those strategies with lower effectiveness and higher costs (dominated strategies) were eliminated from the analysis, and incremental cost-effectiveness ratios (ICERs) were estimated. An ICER is a ratio of the difference in cost between two interventions and the difference in effectiveness of the same two interventions. Its use allows the impact of switching from one intervention to the other to be evaluated.

### **Dealing with uncertainty**

A probabilistic sensitivity analysis (PSA) was performed on all three base-case models in order to incorporate statistical uncertainty into the analysis. This allowed some assessment of the effect on the results of simultaneously varying different parameters. Appropriate parameter distributions were selected, according to the nature of the data, for those input parameters for which suitable data were available. For probability parameters where only two categories of event were possible (i.e. NDI or no NDI) beta distributions were used. All odds ratios were given log-normal distributions and, finally, for those events for which more than two categories of event were possible, a Dirichlet distribution was used in order to account for the polychotomous nature of the variable.<sup>188</sup> The parameter distributions are fully reported in Appendix 8.

### **Formula and donor milk cost for secondary analysis**

The unit costs per litre of donor milk and per 200 ml of preterm formula are presented in *Table 18*. These were not used in the base case, although a second model was evaluated incorporating donor milk costs. It was assumed that infants in the 500–999 g birthweight population commenced feeding on 60 ml/kg, then progressed to 80 ml/kg, then progressed to 120 ml/kg, and then to 150 ml/kg. It was assumed that, for the surgical NEC infants approximately 6.5 days were spent on each feed volume; for the medical NEC infants approximately 4.8 days; for the sepsis infants 4.2 days; and for the no NEC/no sepsis infants 4.4 days. Infants were then progressed to 200 ml/kg for the remainder of their estimated stay in the unit.

It was assumed that infants in the 1000–1749 g population commenced feeding on 60 ml/kg, and then progressed to 120 ml/kg, followed by 150 ml/kg.

**TABLE 16** Length of stay (days) for an infant by birthweight group, illness episode and unit level

	Surgical NEC	Medical NEC	Control	Sepsis
<b>500–999 g</b>				
Level 1	42	27	0	30
Level 2	86	67	62	59
Level 3	86	67	62	59
<b>1000–1749 g</b>				
Level 1	25	16	0	18
Level 2	51	40	37	35
Level 3	51	40	37	35
<b>1750–2500 g</b>				
Level 1	25	16	0	18
Level 2	51	40	21	35
Level 3	51	40	21	35

**TABLE 17** Annual costs of disability states

State	Annual cost (£)
No disability	0
Mild disability	599.07
Moderate disability	599.07
Severe disability	25,759.91

**TABLE 18** Unit costs of formula and donor milk

Milk supplements	Unit cost (£)	Source
200 ml of formula	1.36	BNF <sup>b</sup>
1 litre of donor milk	289.12	BMBWG <sup>a</sup>

a Breastmilk Banking Working Group.<sup>91</sup>  
b British National Formulary.<sup>189</sup>

kg. It was assumed that, for the surgical NEC infants, approximately 4.4 days were spent on each feed volume; for the medical NEC infants approximately 3.4 days; for the sepsis infants 3 days; and for the no NEC/no sepsis infants 3 days. Infants were then progressed to 200 ml/kg for the remainder of their estimated stay in the unit.

For infants in the 1750–2500 g population it was assumed that they commenced feeding at 80 ml/kg and then progressed to 150 ml/kg. For the surgical NEC infants it was assumed that they spent approximately 6 days at each feeding rate; for the medical NEC 5 days; the sepsis group 4.5; and the no NEC/no sepsis 2.5 days.

These estimates are based on length of stay and weight multiplied by the number of ml/kg divided by the number of feeds.

## Results

### Base case

Three populations defined by birthweight were considered in the base-case models. The populations were: 500–999 g, 1000–1749 g and 1750–2500 g. The two alternative feeding supplements – donor milk and preterm formula – were evaluated in separate models for each birthweight population. It was felt that this best reflected the current situation regarding feeding supplementation for this population. Donor milk as a supplement was considered to be the situation in a minority of units in the UK.<sup>91</sup> However, a second model was created with the cost for donor breastmilk supplementation incorporated.

The base-case results of the cost-effectiveness analysis for each of the subpopulations defined

by weight are reported in *Table 19*. In each of the subpopulations, the enhanced staff contact intervention was both less costly and more effective than the comparator, normal staff contact. Enhanced staff contact was the dominating intervention.

The effectiveness of mothers' milk in reducing both the incidence and severity of NEC and sepsis showed positive health impacts for the intervention arm of the model at a reduced cost. Given that the intervention was relatively cheap per infant, consuming only 45 to 195 minutes of staff time, this meant that the cost savings from reduced expenditure on treating NEC and sepsis were always greater than the cost of the intervention. A full breakdown of the cost results per infant are presented in *Table 20*.

**Weight subpopulations**

The incidence of disease was inversely correlated with infant weight, and hence the health benefit and cost savings decreased as the birthweight increased. However, the base-case analysis showed that, despite declining incidence in the heavier populations, the intervention was found to be cost saving.

**Donor milk**

The cost estimate of a litre of donor milk was £289.12. This was the estimate for a milk banking set-up that represented a slight improvement over the milk bank system taken from the UK Breastmilk Banking Working Group report.<sup>91</sup> The model assumed that donor milk was only given to those infants who received some mothers' milk. This may not reflect reality, where an infant whose mother was unable to provide milk may in fact receive 100% donor milk. However, to facilitate modelling, it was assumed that if the mother provided some milk, then in the donor milk supplementation model, the preterm infant would receive donor milk supplements. As the intervention increased the number of mothers expressing, and therefore the number of infants receiving some mothers' milk, logically the results show an increase in cost due to the additional donor milk.

Nevertheless, in the 500–999 g population, the intervention still dominated normal contact. However, this was no longer the case for the heavier birthweight populations (see *Table 19*). For the 1000–1749 g population, the ICER was £3531 per QALY. For the 1750–2500 g population, the ICER was £34,905.

**TABLE 19** Cost-effectiveness results for the base case with formula supplements and with donor milk supplements by birthweight group

	Intervention	Cost (£)	Incremental cost	Benefits (QALY)	Incremental benefit	ICER (£/QALY)
<b>Base case</b>						
500–999 g	Enhanced <sup>a</sup>	86,759		14.70		
	Normal <sup>b</sup>	87,345	586	14.45	–0.251	Dominated
1000–1749 g	Enhanced	56,947		21.05		
	Normal	57,240	293	21.00	–0.056	Dominated
1750–2500 g	Enhanced	47,228		21.92		
	Normal	47,294	66	21.91	–0.009	Dominated
<b>Donor milk supplements</b>						
500–999 g	Enhanced	88,029		14.75		
	Normal	88,107	78	14.46	–0.290	Dominated
1000–1749 g	Enhanced	58,195		21.06		3531
	Normal	57,970	–225	21	–0.064	
1750–2500 g	Enhanced	48,145		21.92		34,905
	Normal	47,816	–328	21.91	–0.010	

ICER, incremental cost-effectiveness ratio.

a Enhanced staff contact.

b Normal staff contact.

**TABLE 20** Cost breakdown for the base case with formula supplements and with donor supplements by birth weight group

	Intervention	Total cost (£)	Intervention cost (£)	Treatment costs (£) until discharge	Long-term disability costs (£)	Donor milk cost (£)
<b>Base case</b>						
500–999 g	Enhanced <sup>a</sup>	86,758	121	55,572	31,065	–
	Normal <sup>b</sup>	87,344	0	56,405	30,939	–
1000–1749 g	Enhanced	56,947	121	38,159	18,666	–
	Normal	57,240	0	38,527	18,712	–
1750–2500 g	Enhanced	47,228	121	22,648	24,458	–
	Normal	47,294	0	22,816	24,478	–
<b>Donor milk supplements</b>						
500–999 g	Enhanced	88,029	121	55,340	31,057	1512
	Normal	88,107	0	56,304	30,942	862
1000–1749 g	Enhanced	58,195	121	38,072	18,649	1353
	Normal	57,970	0	38,490	18,707	772
1750–2500 g	Enhanced	48,145	121	22,619	24,455	949
	Normal	47,816	0	22,799	24,476	541

ICER, incremental cost-effectiveness ratio.  
a Enhanced staff contact.  
b Normal staff contact.

### Uncertainty analysis

A PSA was run for the base case for each of the subpopulations defined by weight. PSA allows the explicit incorporation of parameter uncertainty, as each estimate is defined by an appropriate probability distribution rather than a point estimate. Incremental cost-effectiveness (ICE) scatter plots for each subpopulation are shown in *Figures 35–37*. The vast majority of the estimates were in the bottom-right quadrant, indicating that the intervention was more effective and cheaper than the comparator.

Cost-effectiveness acceptability curves have been produced for the three populations in *Figures 38–40*. These graphs illustrate the probability that the enhanced staff contact intervention has a cost-effectiveness ratio that is lower than the range of cost-effective threshold value values presented on the horizontal axis. For each population it is highly probable that the enhanced contact intervention is cost-effective even at a zero threshold value since the expected costs are expected to be lower for the enhanced intervention and the benefits are expected to be higher.

### Sensitivity analyses

#### Summary

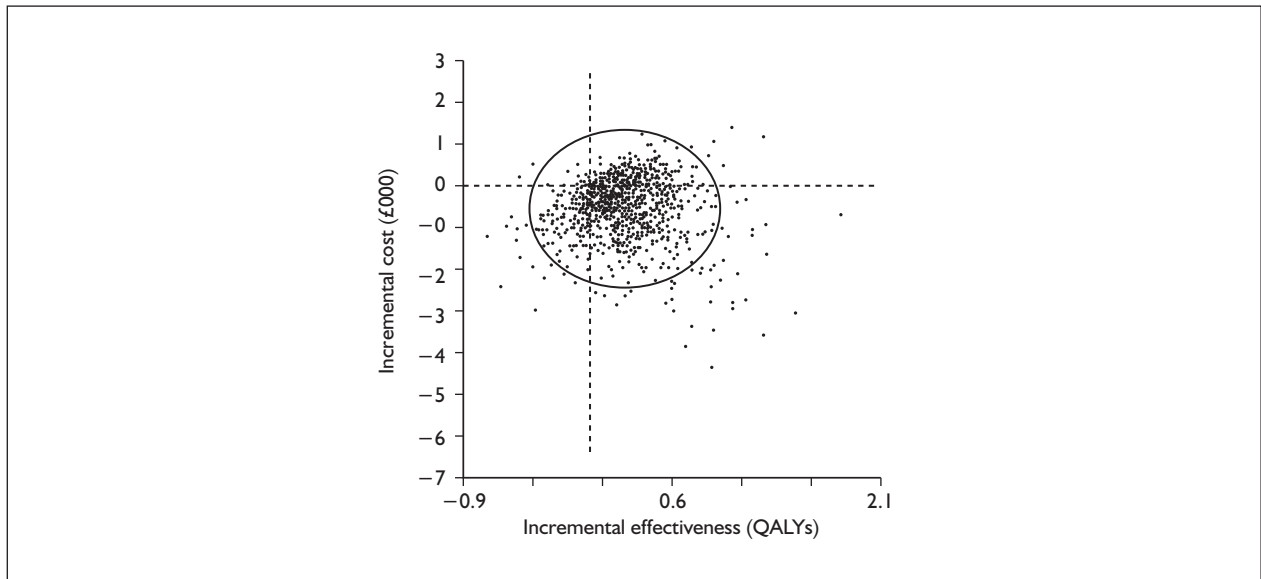
A summary of the main sensitivity analyses is presented here and, in addition, a table presenting the full results of all sensitivity analyses is provided in Appendix 9.

#### 500–999 g population

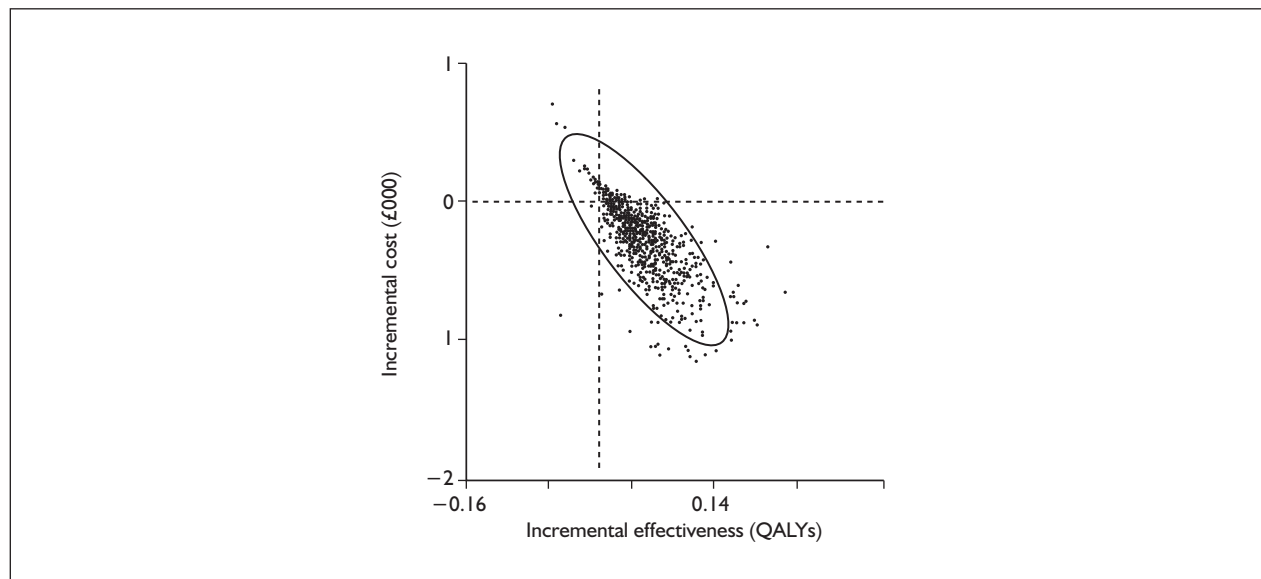
For all sensitivity analyses except for one, the results showed that, in this population, enhanced staff contact was always less costly and more effective than normal contact. The only scenario in which enhanced staff contact was not dominant was where donor milk was provided as a supplement to infants who partially received mother's own milk and both formula and expression kit costs were included as additional costs. The cost-effectiveness ratio in this scenario was £354.68.

#### 1000–1749 g population

The only data input that caused the enhanced staff contact intervention to cease to be dominant was adding the cost of donor milk for those units that used it as a supplement to mothers' milk only. The cost-effectiveness ratios were still very low, with



**FIGURE 35** Incremental cost-effectiveness scatterplot: 500–999 g population.



**FIGURE 36** Incremental cost-effectiveness scatterplot: 1000–1749 g population.

the majority well within what is regarded as the acceptable threshold of £20,000.

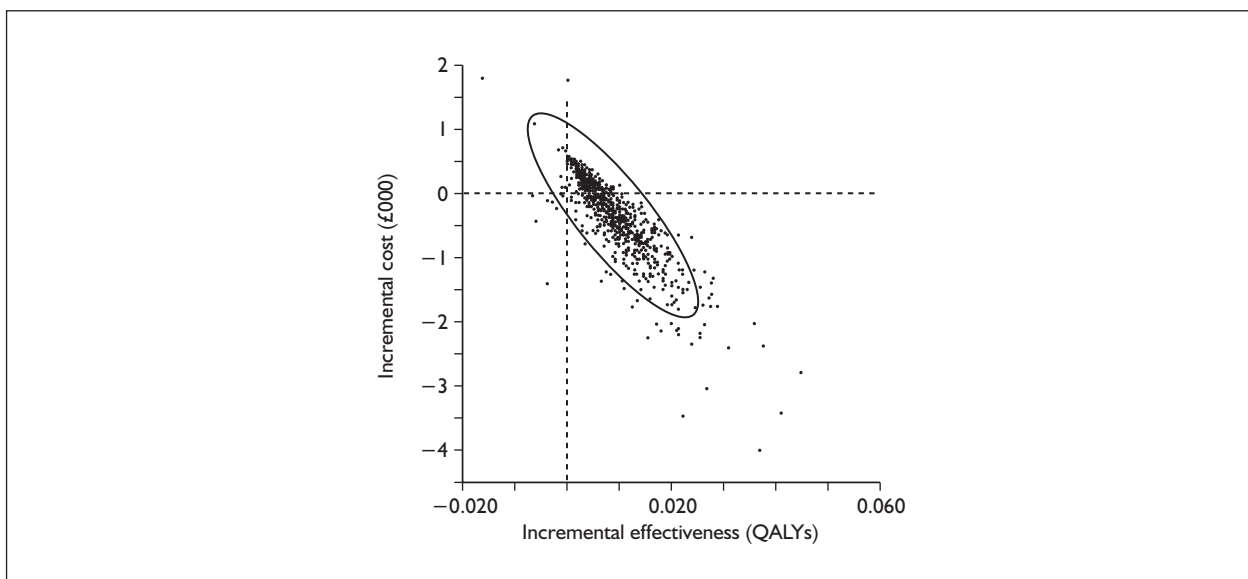
**1750–2500 g population**

For this population, with the exception of the cost of formula, all the cost inputs that were varied made the enhanced staff contact intervention less cost-saving and resulted in the intervention no longer dominating normal staff contact. The ICERs

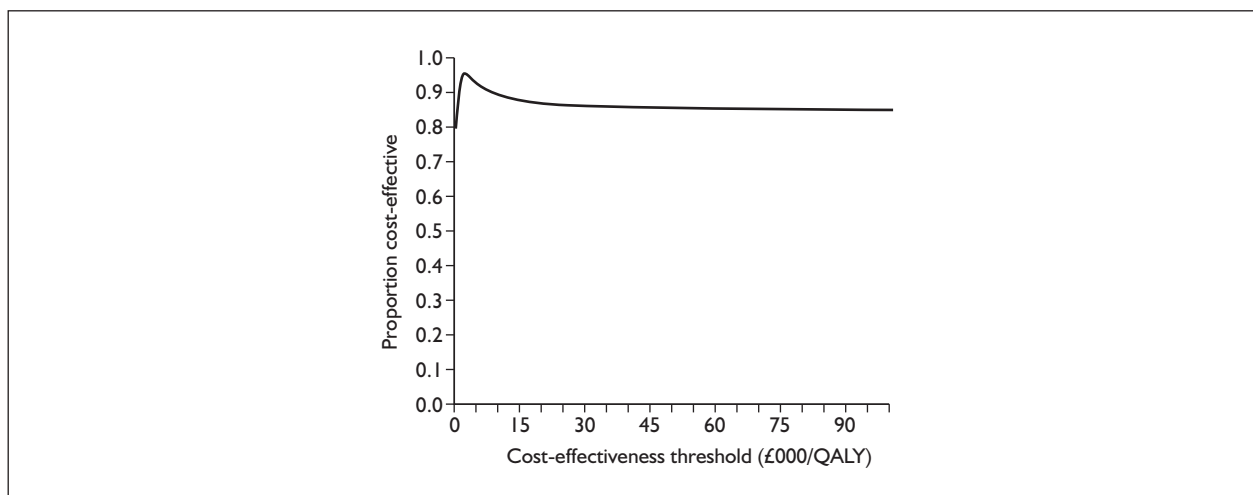
varied from as little as £663 up to £42,302, but the majority were well within the accepted threshold of £20,000.

**Details of analyses undertaken**  
**Intervention effectiveness estimate**

The main intervention effect estimate was derived from two papers identified in the review. The



**FIGURE 37** Incremental cost-effectiveness scatterplot: 1750–2500g population.



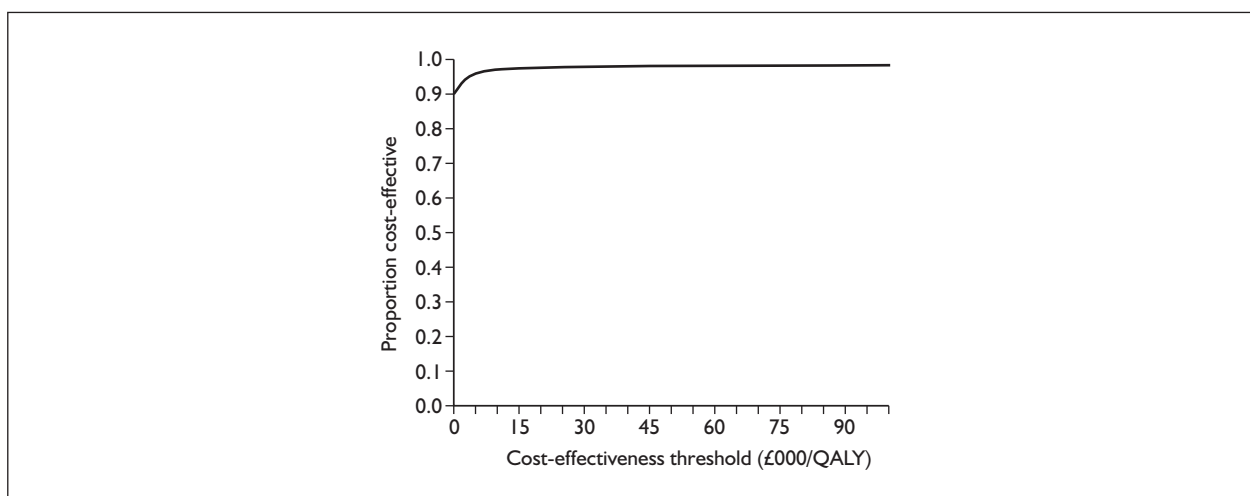
**FIGURE 38** Acceptability curve: 500–999g population.

results of the two papers<sup>149,166</sup> were meta-analysed to produce the base-case intervention effectiveness estimate. As the interventions were not exactly the same and were based on feedback from our clinical advisors, it was decided to conduct the analysis again based only on the lactation consultants and the evidence from Gonzalez *et al.*<sup>166</sup> The resulting effectiveness estimate was only slightly worse in the Gonzalez *et al.* paper<sup>166</sup> than the Pineda<sup>149</sup> estimate, so the intervention was marginally less cost-saving and less effective. In addition, the intervention's effectiveness was assumed to be the same in the base case regardless of the mothers' intentions

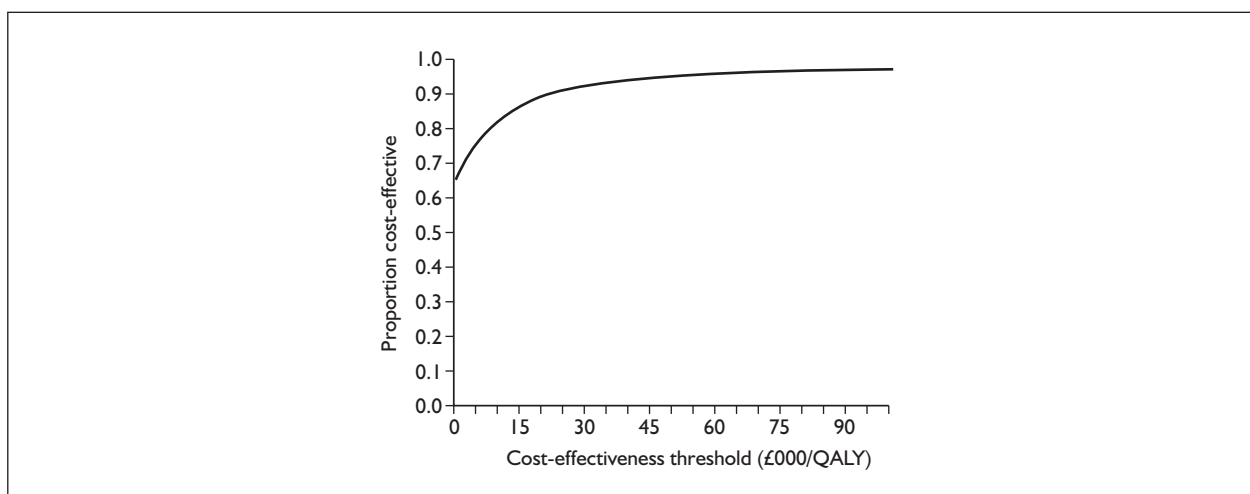
regarding breastfeeding. This assumption was tested in a one-way sensitivity analysis where the odds ratio of an infant receiving mothers' milk was varied over plausible ranges. The results are presented in *Table 21*.

#### **Breastmilk effectiveness estimate**

In the base-case model, the odds ratio of getting confirmed NEC from formula feeding only compared with some mothers' milk and formula was 3.01.<sup>174</sup> Vohr *et al.*<sup>10</sup> provided a significantly lower odds ratio of getting confirmed NEC, namely 1.48. When substituted into the model, this



**FIGURE 39** Acceptability curve: 1000–1749 g population.



**FIGURE 40** Acceptability curve: 1750–2500 g population.

significantly reduced the effectiveness and cost-savings of the intervention, so much so that the intervention became dominated by the comparator for every subpopulation. The results are shown in *Table 22*.

**Intervention cost**

The only intervention cost was the cost of staff time advising and supporting the mothers. In the base case, the unit cost per hour of registered nurse time was used. Registered nurses took the part of lactation consultants in the study of Gonzalez *et al.*<sup>166</sup> The unit cost used was £41.12. It is possible that a midwife might perform the role of lactation consultant, so the hourly unit cost of a hospital midwife was used in a sensitivity analysis, this being

£65.57.<sup>183</sup> The intervention was still dominant for the two lower birthweight populations. In the 1750–2500 g population, the intervention no longer dominated. The ICER was £663 per QALY. The low incidence of disease in this group meant that the cost savings from reduced disease were less than the higher intervention cost.

**Length of stay**

In most of the models, the cost savings due to reduced disease outweighed the intervention costs. The length of stay was the main factor that in the model determined the cost implications of a disease, so the length of stay was halved for each clinical outcome (no disease, sepsis, medical NEC



**TABLE 21** Sensitivity analysis results for different odds ratios of an infant ever receiving mothers' milk for mothers who intended to breastfeed and for those who did not

	Intervention	Cost (£)	Incremental cost	Benefits (QALY)	Incremental benefit	ICER (£/QALY)
<b>0.6 OR<sup>c</sup> for ITB mothers and 0.4 OR for NITB mothers</b>						
500–999 g	Enhanced <sup>a</sup>	86,758.65		14.702		
	Normal <sup>b</sup>	87,275.22	516.57	14.485	–0.217	Dominated
1000–1749 g	Enhanced	56,946.67		21.051		
	Normal	57,193.47	246.8	21.001	–0.049	Dominated
1750–2500 g	Enhanced	47,227.50		21.92		
	Normal	47,272.71	45.21	21.912	–0.008	Dominated
<b>0.4 OR for ITB mothers and 0.6 OR for NITB mothers</b>						
500–999 g	Enhanced	86,758.65		14.702		
	Normal	87,464.03	705.38	14.398	–0.304	Dominated
1000–1749 g	Enhanced	56,946.67		21.051		
	Normal	57,315.95	369.28	20.985	–0.066	Dominated
1750–2500 g	Enhanced	47,227.50		21.92		
	Normal	47,328.00	100.50	21.909	–0.010	Dominated
ITB, intention to breastfeed; NITB, no intention to breastfeed. a Enhanced staff contact. b Normal staff contact. c Odds ratio of infant ever receiving mother's milk in NICU/SCBU.						

**TABLE 22** Sensitivity analysis results for reduced effectiveness of some mothers' milk compared with formula only

	Intervention	Cost (£)	Incremental cost	Benefits (QALY)	Incremental benefit	ICER (£/QALY)
500–999 g	Enhanced staff contact	86,514		14.82		Dominated
	Normal staff contact	86,432	–82	14.90	0.08	
1000–1749 g	Enhanced staff contact	56,783		21.07		Dominated
	Normal staff contact	56,631	–152	21.08	0.005	
1750–2500 g	Enhanced staff contact	47,154		22.36		Dominated
	Normal staff contact	47,019	–135	22.36	–0.002	

and surgical NEC) in each of the three levels of unit.

The intervention still dominated the comparator in the two lightest birthweight populations. However,

it no longer dominated in the 1750–2500 g population. The ICER was £1639.

**Expression kit costs**

The current practice of the provision of breast pumps and expression kits in the UK is not clear. It is likely that, should breastfeeding rates increase, the need for more breast pumps will also increase, but we were unable to cost the impact of the intervention on the provision of breast pumps. Single-use expression kits used in addition to breast pumps are easier to cost, although the overall use of expression kits is not known. Ideally, both the cost of increased breast pump use and expression kit use would be costed, but in this sensitivity analysis only single-use expression kits have been costed.

Adding the cost of ‘single-use’ expression kits increased the cost of the enhanced staff contact. Enhanced contact still dominated in the lower two birthweight populations, but it no longer dominated in the 1750–2500 g population. The ICER of enhanced contact was £5591. The results are shown in *Table 23*.

**Lower donor milk costs**

In the model for donor milk supplements, the cost estimate for a litre of milk was £289.12. This was the estimate for a milk banking set-up that was slightly improved in comparison with the existing milk bank system. It was estimated by the Breastmilk Banking Working Group<sup>91</sup> that, if the milk banking system was significantly reformed and run in a manner similar to the Blood Bank Service, then the cost of producing a litre of donor milk would fall to £119.89. This excluded development costs. This cost was used to estimate the impact of such a reduction in donor milk costs. The reduction in the price greatly increased the cost-

saving potential of the intervention. The lowest population became more cost-saving, the 1000–1749 g population became dominant from having a cost-effectiveness ratio of £3531 per QALY, and the ICER for the 1750–2500 g population reduced from £34,905 to £9500.

**Formula and donor costs**

The consumption of formula should reduce as breastfeeding increases. The cost of formula was excluded as an independent cost item from the base-case model because we were unable to cost the change in use of breast pumps, and both cost items should be included together. Formula costs are included in the unit cost of running a neonatal unit in that hotel services were included and food was a hotel service, but that does not capture the effect of the intervention specifically on the consumption of formula. The cost of formula was therefore included in a sensitivity analysis.

Adding the cost of formula made the intervention even more cost-saving as less formula was consumed as a result of increased milk expression. The intervention became more cost-saving for every population.

Adding formula and expression kit costs to the model had opposite effects and to some extent they neutralised each other, although the expression kits had the greatest impact. The intervention was no longer cost-saving in the 1000–1749 g group. When both were added to the model with donor milk supplied to infants who partially received their mother’s own milk, the enhanced staff contact intervention became less cost-effective due to the high cost of expression kits. In the 500–999 g group

**TABLE 23** Sensitivity analysis results for the addition of the cost of expression kits

	Intervention	Cost (£)	Incremental cost (£)	Benefits (QALY)	Incremental benefit	ICER (£/QALY)
500–999 g	Enhanced staff contact	87,412		14.70		
	Normal staff contact	87,744	332.59	14.45	–0.251	Dominated
1000–1749 g	Enhanced staff contact	57,443		21.05		
	Normal staff contact	57,543	100.27	21.00	–0.056	Dominated
1750–2500 g	Enhanced staff contact	47,523		21.92		
	Normal staff contact	47,474	–48.64	21.91	0.009	Dominated

enhanced staff contact was no longer dominant, with a cost-effectiveness ratio of £355. In the 1000–1749 g group the cost-effectiveness ratio rose from £3531 to £5550. In the 1750–2500 g group the cost-effectiveness ratio rose from £34,905 to £42,301.

Both formula, at a cost of £1.36 per 200 ml, and supplementation with donor milk, at a price of £289.12 per litre, were included in the model together. This analysis was appropriate for the units that currently use donor milk as a supplement to mothers' milk. The cost-saving effect of formula costs in the model caused the intervention to be more cost-effective with the ICER of enhanced contact reducing to £2533 from £3531 for the 1000–1749 g group and to £30,113 from £34,905 for the 1750–2500 g subgroups.

Adding formula costs to the model with the lower donor costs halved the cost-effectiveness ratio to £4690.

#### **Incidence of mothers intending to breastfeed**

In the base case the incidence of mothers intending to breastfeed prior to childbirth was 72%. This was the value for England in the Infant Feeding Survey 2005. In sensitivity analysis this was changed to 56%, the value for Northern Ireland. It was also varied from 50% to 90% to cover rates for different

ethnic groups. An increase in the intention to breastfeed rate increased the health benefits of enhanced contact and increased cost-saving (see *Table 24*). This is the result of two factors. Firstly, the infants of mothers who intended to breastfeed would end up consuming more mothers' milk than infants whose mothers did not intend to breastfeed given an enhanced contact intervention. Secondly, the effectiveness of an enhanced contact intervention was assumed to be the same for both mothers who intended to breastfeed and those who did not and, in reality, this may not be the case. This assumption was tested in sensitivity analysis and the results are also presented in *Table 24*.

#### **Lower disability rate for 1750–2500 g group**

In the base case, the rate of severe disability was higher for the 1750–2500 g group than for the 1000–1749 g group. This was the result of the data in the Larroque paper.<sup>180</sup> However, as this appeared to be counterintuitive, on the advice from our clinical experts the probability of severe disability given some disability was reduced to 5% from 14.1% for the 1750–2500 g group. Correspondingly, the probability of mild disability given some disability was increased from 65% to 74.1%. This made the enhanced support only slightly less beneficial and cost-saving; the enhanced staff support still dominated normal support.

**TABLE 24** Sensitivity analysis results for different incidences of intention to breastfeed (1000–1749 g population)

ITB incidence	Intervention	Cost (£)	Incremental cost (£)	Benefits (QALY)	Incremental benefit	ICER (£/QALY)
50%	Enhanced staff contact	57,033		21.04		
	Normal staff contact	57,305	271.97	20.99	-0.052	Dominated
56%	Enhanced staff contact	57,009		21.04		
	Normal staff contact	57,287	277.72	20.99	-0.053	Dominated
72%	Enhanced staff contact	56,947		21.05		
	Normal staff contact	57,240	293.04	21.00	-0.056	Dominated
90%	Enhanced staff contact	56,876		21.06		
	Normal staff contact	57,187	310.27	21.00	-0.059	Dominated



# Chapter 6

## Lessons from clinical practice

### Background and methods

It is uncommon for neonatal units to have high rates of breastfeeding/breastmilk feeding. As a result, there is a possibility that important research questions have not been addressed at all, or that the use of specific interventions in practice may not be fully understood. To help set the findings of this evidence review in context, to inform the social and organisational context for generalisability of effective interventions to UK settings, and to inform discussion on research priorities, we sought the views of a group of clinical experts who work in neonatal units where breastfeeding/breastmilk feeding rates are high.

Seven experts who worked in neonatal units where breastfeeding/breastmilk feeding rates were known to be high were identified through professional networks, including reading published literature and recommendations by Advisory Group members; two were already members of the Advisory Group. They were approached informally using a range of methods, including face to face, telephone and email. They were asked for their responses to a standard set of questions, which included:

- description of their neonatal unit and the population served
- description of breastfeeding/breastmilk feeding-related practices, to include history of developments, obstacles to change, supportive factors, and practices that had worked
- finally, they were asked what advice they would give to other units where staff wished to increase breastfeeding/breastmilk feeding rates.

### Findings

#### Description of the units

Five units were in the UK, one in Sweden and one in the USA. The units included intensive care/high dependency, special care and transitional care settings. Units cared for populations that were mainly inner city, metropolitan or urban, and socially deprived, with only one unit serving a middle-class area. All had significant ethnic

minority or refugee/asylum seeker populations. Five reported that most of their previous problems with breastfeeding/breastmilk feeding had been addressed and developments were now sustained; two UK units indicated that there were signs of improvement and there was the potential for sustained change. Five units had started work to improve breastfeeding in 1996 or before, with one indicating that they had started work on this issue since 2000. This information was not available for one unit.

#### The change process

All units reported that the work had been led by an individual specifically tasked to co-ordinate the changes. Five reported that this was an infant feeding specialist: in one case, this infant feeding specialist was working in conjunction with a consultant neonatologist, and in another the specialist was also a senior neonatal nurse with an academic background in breastfeeding. In one case, the change was led by a senior nurse.

The support of other staff was reported to be critically important. Units reported support and engagement by a range of staff, including clinical directors, general managers, service managers (medical and nursing), unit managers, senior neonatologists, neonatal nurses including nurse practitioners, midwives, the NHS trust breastfeeding co-ordinator, and the trust breastfeeding group. The US unit established a 'Mother's Milk Club' to engage mothers themselves in the programme of change.

Five units reported that there was opposition to the changes, some of it transient, some longer lasting. This took the form of continued adherence to previous routines such as restrictions on feeding, routine supplementation, and bottles at night, also opposition to giving responsibility for feeding to mothers, and staff not liking the specialist role, thinking initially that it disempowered other staff. They also reported that neonatal nurses did not like consultants making changes, that it took a long time to change attitudes, that there was a perception that infants took longer to breastfeed, and that intensive care staff were rarely able to help

with breastfeeding due to their work with critically ill infants. Some units reported that changes took several years. One unit reported that very rapid changes were possible, with the lactation initiation rate rising from 17% to 73% within 3 months of an integrated change programme.

### Barriers to change

Several important barriers to change were reported. These included:

- Lack of a coherent approach among staff:
  - a lack of communication/co-ordination between staff groups, including neonatologists, neonatal nurses, and midwives
  - an assumption among neonatal unit staff that postnatal and community midwives would deal with mothers and expression of breastmilk
  - an assumption among medical staff that feeding was a nursing issue
  - lack of support for change introduced by a nurse rather than by a doctor
  - a lack of compliance with breastfeeding/breastmilk-feeding policy and apathy among staff.
- Lack of knowledge and belief in breastfeeding/breastmilk feeding among staff:
  - a lack of knowledge of the evidence base and clinical skills in helping mothers and infants
  - a lack of knowledge of breastfeeding/breastmilk feeding, and associated belief in the mother and infant's ability, including a belief that infants became exhausted by breastfeeding and a lack of belief in infants' nutritive sucking ability.
- Problems with facilities/the environment of the neonatal unit, including:
  - lack of privacy/screens/comfortable chairs/space for parents
  - lack of parent rooms for 24-hour stay
  - lack of pumps and funnels for expressing, in hospital and at home
  - infants being disturbed by the noise of other parents, staff
  - workforce problems resulting in nurses looking after more than one sick infant, with no time for feeding/support for mothers.
- Mothers being at a distance once they were discharged home.

### Factors supporting change

The main factors identified that helped in creating the necessary change, and factors that the experts would advise other units to consider, fell into seven main categories. Units indicated that an integrated approach was needed across all of these. They were:

- staff behaviour, training and co-ordination
- audit and feedback of outcomes
- involving parents
- clinical practices
- organisation of care
- facilities
- funds and resources.

Details of these categories are listed under the respective headings.

#### *Staff behaviour, training and co-ordination*

- Leadership: a dedicated role was needed, supported by a core group with expert knowledge.
- A consistent, evidence-based feeding policy and guidelines; including
  - evidence-based information on the differences in lactation physiology between term and preterm mothers, and on the science of milk expression, milk composition, and infant feeding including unrestricted feeding, support for frequent feeding, and a gradual reduction of supplements
  - focus on breastmilk as medicine, with evidence for improved health outcomes.
- Effective evidence-based education and training for all staff, including senior staff, with mandatory training and annual updating and monitoring of consistent use of policy/guidelines.
- Support from senior neonatologists.
- Good communication.
- Using a team approach.
- A gradual acceptance: nurses saw that it was possible and experienced success, then they convinced neonatologists.
- Improvements valuable for staff morale.

#### *Audit and feedback, with benchmarking*

- Measuring dose and exposure period of breastmilk, as well as duration outcomes.
- Measuring health outcomes for infants.

#### *Involving parents*

- Responding to mothers' requests for change.

- Giving mothers evidence-based information on the importance of breastmilk for their infants, and on ways of maximising milk production.
- Empowering mothers to believe in themselves and their infants.
- Information and practical help for mothers.
- Support for skin-to-skin care.
- Bottles given only with mother's permission.
- Entrusting care to parents as soon as possible.
- Supportive environment, screens for privacy, bed for parents beside the infant.
- Training mothers who have been in neonatal unit as peer counsellors.
- Supporting father's presence.
- Decreasing noise in parents' rooms to encourage sleep.

#### ***Clinical practices and organisation of care***

- Using creatinocrits and test weights to diagnose and manage problems and reinforce understanding of lactation for both staff and mothers.
- Moving to total daily volume measurement instead of scheduled feeding, and giving mothers the milk volume records to keep themselves.

- Focus on importance of providing breastmilk if mothers do not plan to breastfeed.

#### ***Organisation of care***

- Programme for early discharge plus open-door policy if problems post discharge.
- Training and appointment of peer counsellors.

#### ***Facilities***

- Modifications to physical environment to enable ongoing contact between mothers and infants.
- Freely available good-quality breast pumps.
- Suitable environment in which to express milk.
- Assistance with transport from home to hospital.
- Access to milk bank.
- Purchase of suitable clothing for mothers to enable skin-to-skin care.

#### ***Funding and resources***

- Funds for resources and staff time to support all changes.





# Chapter 7

## Summary and discussion

This systematic review and economic analysis has examined the effectiveness and cost-effectiveness of interventions to enable women to breastfeed/give breastmilk to their infants despite the challenges of starting life in a neonatal unit. New evidence has been identified to inform care and future research, and the economic analysis conducted is the first in this complex and important field and offers a model for future decision analysis.

### Effectiveness review: overview, strengths and limitations

The effectiveness review identified a total of 48 studies related to breastfeeding or feeding with breastmilk for infants in neonatal units. Studies were conducted from 1984 to 2007. They included 31 RCTs (65%), three randomised crossover studies (6%) and 14 other forms of controlled studies (29%); the inclusion of this range of study designs was considered important in a field where RCTs have not always been conducted and may not always be possible.

This work was intended primarily to inform those working in UK settings. However, it was recognised that there may be lessons to learn from those living in situations where breastfeeding is the norm and hence studies were not excluded on the basis of country. Included studies were conducted in 17 countries: 11 resource-poor countries, and six industrialised countries. Eight studies (16%) were conducted in the UK, including six RCTs – 26% of all the included RCTs. It is likely that the findings will be appropriate for those in countries with systems of care and breastfeeding rates similar to those in the UK, and findings from some studies may also have some value for those working in very different countries.

### Strengths

This review was based on a comprehensive search, updated in January and February 2008, with additional studies identified by experts in the field. Through this process we identified 19 studies that

were not already included in systematic reviews. We are aware that other studies may exist that have not been identified through this process.

All the included studies tested interventions with appropriate control groups. Each study was assessed for quality according to appropriate parameters for that design, and details of each study are presented accordingly in tables and in the text. The review has identified a wide range of studies, and the review team has worked to ensure appropriate analysis and conclusions. Details of included studies have been given in the data extraction and quality appraisal forms (*Tables 26–73* in Appendix 4.1 and *Tables 74–87* in Appendix 5). We have endeavoured to present methods and results in as transparent a manner as possible, avoiding findings that may be misleading. Wherever possible, results have been presented using intention to treat (ITT) analyses, adjusting for postrandomisation exclusions as appropriate. When results are shown in forest plots, studies rated as 'poor' have been omitted.

Studies included have examined a wide range of interventions, including clinical, health promotion and staff training interventions. This comprehensive perspective is essential in this topic area. Factors making breastfeeding difficult in neonatal units in the UK, as outlined in Chapter 1, are complex and multifaceted, and intervention to raise the rates is likely to require a range of different measures and an integrated approach.

The research team have backgrounds related to maternal and child nutrition including breastfeeding, public health nutrition, midwifery, neonatology, health economics, health services research and health policy, and we were supported throughout by expert academic, clinical and service user colleagues from the UK and internationally. This input was essential as breastfeeding remains a challenge in many neonatal units in the UK<sup>46</sup> and abroad. Expertise and input from practitioners working in units where breastfeeding/breastmilk feeding rates are high, and from women with experience of having infants cared for in neonatal units, were needed to assist the questioning of current practice and

in the interpretation of evidence. These views have been described in Chapter 6, and we have drawn on these experiences to reflect on the findings of this research, to inform the social and organisational context for generalisability of effective interventions to UK settings, and to help to shape the research agenda. We have also had important input from service user members of the Advisory Group, and we have used the literature that reports the views of women and families whose infants have been cared for in neonatal units in different settings (summarised in Chapter 1) to identify current experiences and wishes of families that might inform the research agenda.

## Limitations

The main limitation of the review is the scarcity of high-quality research identified; only seven studies (15%) were assessed as good quality. In addition, studies were extremely heterogeneous in terms of characteristics of the interventions, controls or standard care, participants and outcomes reported. Meta-analyses have not been conducted on any topic as a result. This is discussed in relation to each section, and lessons learned for future research are discussed in Chapter 9.

Many studies were conducted in settings where breastfeeding rates in the population were low. Although this could support generalisability of such studies to a UK setting, this is a challenge for the interpretation of the findings of this review, as the interventions may have a different impact in settings where population rates are high, staff are familiar with and trained in supportive practices, families expect women to breastfeed, and infrastructure such as milk banking is in place.<sup>190</sup>

An important eligibility criterion for this review was that infants were cared for in neonatal units at some stage, even if they were studied post discharge. There is inconsistency internationally in admission to neonatal units: some infants who are cared for in postnatal wards might, in other settings, be admitted to a neonatal unit, and vice versa. The same issue applies to admission to special versus intensive care, and for this reason we did not distinguish between infants admitted to these settings in our analysis. We may for this reason have excluded some relevant studies of preterm or low birthweight infants who were cared for outside a neonatal unit setting, including primary care settings.

A further limitation of the evidence base was the absence of studies that evaluated the effect of support from family members. One study reported fathers' views of the intervention (Pinelli *et al.*<sup>126</sup>) and another included fathers in the assessment of parental anxiety as a result of the intervention.<sup>109,110</sup> A further two studies<sup>121,141</sup> included fathers as part of the intervention but results were reported for mothers only.

An important feature of this work was the iteration between the findings from the formal evidence base and the Advisory Group and clinical experts. This was considered to be necessary in a field where the evidence base was limited and heterogeneous, and where relevant skills and experience are limited in current practice. The intention was to use the strengths of the Advisory Group and clinical experts in both the topic area and study methodology. It is, however, possible that bias was introduced as a consequence. To address this, we have been both cautious and transparent in our use of information gained in this way.

## Effectiveness review: summary and discussion

### Increased mother and infant contact interventions

This section examined studies of additional contact between mother and infant, over and above standard care. 'Standard care' in these studies and in many neonatal units involved a high degree of separation between mothers and infants, and very limited opportunity for the intimate contact, including skin-to-skin contact of any form, that mothers of healthy infants would enjoy without the need for intervention. The evidence base was limited; none of these studies was rated as good quality overall.

All studies evaluating mother and infant contact were interventions of kangaroo skin-to-skin contact, kangaroo mother care (KMC) or skin-to-skin care, representing the largest category of breastfeeding promotion interventions examined in this review (12/48, 25%). The timing and duration of contact varied across the studies and between participants (see *Table 3*). All studies examined infants who were described as clinically stable. Several studies included twins and multiple births, but none reported analyses separately for these mothers and infants.

No studies reported rates of initiation of breastfeeding or oral feeding of expressed breastmilk.

Five studies<sup>115,121,135,141,147</sup> evaluating kangaroo skin-to-skin contact showed increased duration of any breastfeeding prior to, at or up to 1 month after, hospital discharge. These studies were similar in several respects; a mostly short (i.e. including 10 minutes, 1 hour and at all visits) or medium (i.e. including two 4-hour periods) level of daily contact was implemented during the period of hospital stay among a population group of clinically stable infants of mainly very low birthweight in industrialised settings, including the UK. The limited psychosocial data available suggest that a medium level of contact may not be acceptable to mothers in the USA, although the findings of a recent trial, published outside the parameters of this review, question this.<sup>159</sup> The majority of mothers in a variety of industrialised settings, including the UK and USA, appeared to be willing to comply with short levels of kangaroo skin-to-skin contact. These findings may reflect cultural issues associated with countries with typically low breastfeeding rates and may vary in different cultural settings. They may also be modified with antenatal and postnatal education and support by staff. Further information is needed to explore the views and experiences of mothers and staff in regard to kangaroo skin-to-skin contact, as psychosocial data are limited in these studies.

Kangaroo skin-to-skin contact was effective among all mothers regardless of feeding intention, although greater gains may be achieved among women who intend to breastfeed their infants.<sup>115,141,145</sup> These findings of effectiveness were also demonstrated in a recent RCT published outside the search dates for this review (see Appendix 10).

One study found no positive benefit on duration of any breastfeeding at 40–41 weeks' corrected age.<sup>107</sup> This study was different in two key respects: the intervention was more comprehensive including prolonged (i.e. including 20 or 24 hours or until the infant can no longer tolerate contact) kangaroo skin-to-skin contact, early discharge and regular breastfeeding; and it was conducted in a resource-poor country setting where breastfeeding rates in the population were high.

All studies that evaluated rates of exclusive breastfeeding at various time points were

conducted in resource-poor country settings. Only one site in one study identified a positive effect on this outcome, and caution is required in interpretation of these findings due to methodological constraints.<sup>131</sup>

Six studies conducted in both industrialised<sup>115,121,141</sup> and resource-poor<sup>107,118,131</sup> country settings examined health outcomes. These included infants of very low birthweight in industrialised settings and primarily low birthweight infants in resource-poor country settings. They showed statistically significant improvements for the rate of head circumference growth, oxygen saturation, hypothermia and serious morbidity at 2 and 6 months.

All trials reported no adverse effects as a result of kangaroo skin-to-skin contact, with or without early discharge from hospital, for infants of low or very low birthweight when compared with standard care.

#### **Mother and infant contact: conclusions**

From the findings of our review, the effects of kangaroo skin-to-skin contact on breastfeeding in industrialised countries can be stated with some confidence. Short (i.e. including 10 minutes, 1 hour and at all visits) periods of skin-to-skin contact increase the duration of any breastfeeding up to 1 month after hospital discharge among clinically stable, very low and low birthweight infants. This effect is likely to be seen regardless of mothers' feeding intentions prior to and at hospital discharge, although more prolonged increases in duration of any breastfeeding are likely among mothers who intend to breastfeed. Short exposure to kangaroo skin-to-skin contact during the hospital stay is feasible and acceptable to mothers in industrialised settings where breastfeeding is not the cultural norm. The provision of personal breastfeeding education and support by a skilled nurse as an integral part of the intervention is likely to increase the success of the intervention both in terms of breastfeeding outcomes and the acceptability of higher levels of skin-to-skin contact among women who intend to breastfeed their preterm infant.

Prolonged levels (20 or 24 hours per day) of kangaroo skin-to-skin contact are not likely to increase further the exclusive breastfeeding rates among clinically stable infants with birthweights of less than 2000 g in resource-poor country settings. Impact on the duration of any breastfeeding is inconclusive.

Daily use of kangaroo skin-to-skin contact, for short, medium or prolonged duration, is associated with improved health outcomes including the rate of head circumference growth, oxygen saturation, thermal stability and serious morbidity at 2 and 6 months for infants of less than 2000 g in both resource-poor countries and industrialised settings. Based on the limited data available from resource-poor country settings, medium and prolonged levels of skin-to-skin contact are less expensive than standard, incubator care.

These findings are supported by the views of the clinical experts subgroup as reported in Chapter 6. They reported that two important factors in increasing breastfeeding/breastmilk feeding rates in their neonatal units were close contact between mother and infant, and the involvement and empowerment of mothers in caring for their infants. This in turn is supported by the qualitative literature on mother–infant contact reported in Chapter 1, and by the views of consumer members of the Advisory Group. Skin-to-skin contact, and particularly kangaroo skin-to-skin contact, offers mothers and infants the experience of a close, intimate relationship, and mothers an opportunity to take responsibility for the care of their infant on a regular basis.

It is important to note that although parental contact with infants on neonatal units in the UK is less than many families wish, and facilities for ongoing, close contact are limited in many units<sup>43</sup> there is relatively more visiting and parental involvement in the UK than in many other European units,<sup>191</sup> offering greater potential for the introduction of interventions to promote skin-to-skin and other forms of breastfeeding promotion contact.

In the light of the potential for this intervention to have important positive consequences for mothers and infants, important questions remain about the transferability of this intervention to UK neonatal units, and this is discussed further in Chapters 8 and 9.

### Interim feeding methods and related interventions

This section examined methods of feeding for the infant until feeding from the breast is possible, and included related interventions that may support or interfere with transition to the breast. Five RCTs,<sup>119,120,122,124,130</sup> and one crossover study<sup>136</sup> were identified that measured breastfeeding outcomes.

Of these six studies, only one was rated as good quality,<sup>119</sup> and that one had significant compliance problems.

All studies recruited infants who were well enough to tolerate enteral feeds, excluding those with congenital difficulties. Some studies included multiple births, but none presented analyses separately for these mothers and infants.

Findings from the four trials of cup versus bottle feeding<sup>119,120,122,124</sup> indicate that cup feeding increases exclusive breastfeeding at discharge compared with standard bottle feeding. There is possibly a concomitant delay in discharge for cup-fed infants but these results are confounded by hospital policy and poor compliance. Episodes of severe oxygen saturation were increased in the bottle-feeding group in the sole trial to report this parameter. In addition to the compliance problems, confounding factors including the use of pacifiers and caregivers' fingers for non-nutritive sucking, require consideration. More substantively, bottle feeding was the standard technique used in all included trials, and both staff and mothers were less familiar with cup feeding. Results are very likely to have been affected by the lack of familiarity with this novel intervention.

No good or moderate quality studies of nasogastric versus bottle feeding were identified, and no conclusions can be drawn. No effect of pacifier use on breastfeeding outcomes has been identified. There is no evidence that use of caregivers' fingers in place of pacifiers improves or worsens breastfeeding outcomes. One small crossover study of moderate quality found that milk transfer was increased at the feed where mothers with breastfeeding problems used an ultra-thin nipple shield.

### Interim feeding methods and related interventions: conclusions

One previous systematic review by Flint *et al.*<sup>163</sup> reached very different conclusions from the other two previous reviews<sup>155,161</sup> in suggesting that cup feeding should not be used and further research be considered futile. On the basis of the findings from our review, we cannot support Flint's conclusion. Our interpretation of the limited but important evidence is that cup feeding can be used in neonatal units as an alternative to bottle feeding for clinically stable infants who are ready for oral feeds, but only in settings where staff are adequately trained and mothers wish to use it. In such circumstances it is likely to increase

exclusive breastfeeding at discharge and reduce the frequency of oxygen desaturation when compared with infants fed by bottle. This latter finding is supported.<sup>192</sup> A further consideration is the simplicity of cleaning cups as opposed to bottles and teats, potentially reducing the risk of nosocomial infection;<sup>193</sup> this risk will be greater in resource-poor settings.

Questions remain, however, about two important issues: the optimum techniques to use for both bottle and cup feeding to promote appropriate feeding behaviour and optimise the transition to breastfeeding (with associated staff training implications); and whether or not cup feeding can sustain the nutritional intake needed – spillage of breastmilk from cups is an important factor that makes the measurement of nutritional intake difficult.<sup>98</sup>

Encouraging oral feeding in preterms is dependent on the co-ordination of sucking, swallowing and breathing.<sup>93</sup> Oral feeding of infants requires caregivers to be aware of and responsive to infant cues related to this. No studies specifically examined this important issue.

There are safety concerns associated with the use of both nasogastric and orogastric tubes in preterm infants that should be considered in any future research of their use in this field.<sup>194</sup>

Findings are inconclusive for the use of pacifiers and caregivers' fingers for non-nutritive sucking. The fact that one study used caregivers' fingers without noting this as a specific intervention<sup>122</sup> indicates that this practice may be viewed as harmless. Related to this issue, authors of a study identified in another section of this review<sup>138</sup> noted that they introduced 'finger feeding' – where a feeding tube leading from a container of milk is attached to the caregiver's finger and inserted in the infant's mouth – across both groups in their trial without citing experimental evidence to support its use. Theoretically, the insertion of fingers into the mouth of an infant could have at least as big an impact on future feeding behaviour as pacifiers, and in the absence of evidence should not be accepted as a more effective or safer intervention. Non-nutritive sucking is very important for infants who cannot feed directly from the breast, and important questions remain in relation to practices that might impact positively or negatively on future breastfeeding and other clinical outcomes.

Feeding infants effectively and in ways that encourage early transition to the breast is fundamental to enabling breastfeeding in this population. There is very little evidence to guide health professionals or parents in this area, and important research questions remain to be addressed. This suggests that enabling early feeding from the breast is important, and increased mother–infant contact may have a role to play in this. This is discussed further in Chapters 8 and 9.

## Expressing breastmilk interventions

This section examined the use of different techniques, equipment and regimens to assist mothers with milk expression. Six studies contributed findings: five RCTs,<sup>112,114,124,128,142</sup> and one randomised crossover study.<sup>134</sup> Four were conducted in industrialised countries, with two in the UK.<sup>114,125</sup> Participants were from socioeconomically mixed groups. Twins and multiples were included in some studies, but data are not reported separately for these. Only one trial was rated as good quality,<sup>125</sup> and three were moderate.<sup>114,128,142</sup> Lack of compliance was reported to be an issue, even in the good-quality study.<sup>125</sup> Trials examined a wide range of techniques, equipment and regimens; each study tested a unique combination.

Double or simultaneous pumping was found to be more effective than single pumping or a hand pump in the first 2 weeks in the UK and in Nigeria.<sup>114,142</sup> In regard to later time periods, no differences in milk production were found between single versus double expression with an electric pump, or using a novel hand pump versus another electric pump.<sup>125,128</sup> Three studies<sup>114,125,128</sup> reported that simultaneous pumping took mothers less time than sequential pumping. This is likely to be welcomed by mothers whose time may be limited by other commitments, and who may be tired and stressed.

Only one study reported health outcomes for mothers, such as nipple damage and mastitis.<sup>125</sup> Such adverse events are likely to occur in these mothers, and can have a major negative impact on their motivation to continue with an already difficult task. It has been noted that pumps may not have different flange sizes to fit different breast sizes, and this can cause serious trauma.<sup>21</sup> No experimental studies of different types of flange sizes or inserts were identified. Data on mothers' views are sparse.

Details of care of the mothers and infants including factors that may have acted as co-interventions were lacking. Cost-effectiveness outcomes were not identified.

### **Expressing breastmilk: conclusions**

The expression of breastmilk is key for virtually all mothers of infants in neonatal units, and it is a practice that may have to be continued for weeks or even months by mothers of infants who are very preterm or sick, requiring high levels of motivation on the part of the mother and those supporting her. Identifying simple, comfortable, efficient and effective procedures could make a very important contribution to this aspect of care.

This evidence suggests that double pumping with a hospital-grade electric pump with suitable silastic inserts to prevent injury to mothers has advantages over other methods in the first 2 weeks. However, once the mother is discharged home, she may require pumps both at home and in hospital during her visits to the infant. At this stage, she may benefit from using other methods such as a hand-operated pump, or hand expression, for milk removal at home, as well as continuing to use the hospital pump when she is there. Hand pumps may have practical advantages for the mother as well as being cheaper, potentially increasing scope for more widespread provision by neonatal units within limited budgets.

No studies examined milk quality in relation to method of pumping; for example, the foremilk/hindmilk ratio may be affected by hand versus suction pumping. Most existing electric pumps work using a standard suction/release mechanism, which is unlike the pattern of sucking used by infants. Since the conduct of the trials included in this review, a novel type of pump that aims to mimic the sucking pattern of the infant has been developed (Medela Symphony® pump). Published experimental research on this pump is not yet available although a study by Meier *et al.* is forthcoming. Examination of the quality as well as the quantity of milk is important.

None of the trials prescribed an amount of milk to be expressed. The reported increases in milk production during the first 2 weeks as a result of double pumping may be important in order to build reserves of breastmilk and maternal capacity to continue producing milk in later weeks. Two papers<sup>195,196</sup> have suggested setting a goal for daily milk volume of around 750 ml/day to encourage mothers to continue to express on a regular

basis. This consideration further supports the use of double pumping during the first 2 weeks to promote sufficient mother's own milk both to meet the needs of her newborn preterm infant and to establish lactation.

Only one study<sup>125</sup> presented outcomes separately for mothers of twins and multiple births. Achieving optimum milk production is even more important for these mothers, whose milk is needed by more than one infant.

Expression may be used by different mothers for different purposes and this may confound study findings. Some mothers may wish to express to establish lactation and continue to breastfeed over time, while others may wish to provide milk only until the infant is discharged home. A subgroup analysis within one study<sup>125</sup> found that mothers who attempted to breastfeed had a significantly higher number of expressions and volume expressed than mothers who did not attempt to breastfeed. This reflects the important issue, identified in other sections of this review, that increasing the number of women who want to start to breastfeed could have a positive impact on breastfeeding outcomes.

Issues related to regimens for milk removal, such as how often, how long and how much to express, are addressed further in the following section (see Additional interventions to enhance breastmilk production).

As described in Chapter 6, the clinical expert subgroup identified effective milk expression, starting from soon after birth, as fundamentally important both to provide mother's own breastmilk for the infant and also to maximise milk supply for when the infant is able to take the breast.

It is evident that milk expression is a practice that is likely to be influenced by factors other than the use of a pump. Other interventions included in this review, including skin-to-skin contact, interventions to enhance milk production, support and staff training, are all likely to have an impact, as are attitudes of staff, time constraints and psychological factors. Only one included study examined co-interventions – i.e. breast massage before pumping.<sup>114</sup> As well as implementing the interventions identified here, therefore, there are important implications for the education and support of women who are expressing milk for prolonged periods both in hospital and at home, for staff training and for the organisation of care. Women need to be enabled to use appropriate

equipment including pumps, correctly sized flanges and soft inserts to prevent trauma to their nipples and breasts, and to have suitable facilities in which to express. Such a multifaceted supportive system has been described by Meier *et al.*<sup>21</sup>

Important questions remain about the optimum ways to enable women to produce adequate breastmilk for their infants, both to sustain the infant while in the neonatal unit, and to establish adequate lactation for the longer term. This is discussed in Chapter 9.

### **Additional interventions to enhance breastmilk production**

Seven studies were identified that examined this topic.<sup>114,123,133,144,146,148</sup> Five were RCTs and two were randomised crossover studies. All were conducted in industrialised countries. One was rated as good quality,<sup>144</sup> the others as moderate quality. No study intended to recruit women of a particular age, socioeconomic background or parity. Studies did recruit twins and multiple births, but results are not reported separately. Studies predominantly measured short-term milk volume outcomes, and there was limited assessment of breastfeeding/breastmilk feeding exclusivity or duration, or of breastmilk composition. There was no evidence of effects on breastmilk fat or breastfeeding duration of any intervention based on the findings of these seven studies.

There is no evidence that oxytocin spray or metoclopramide has an effect on breastfeeding/breastmilk feeding outcomes. There is very limited evidence that domperidone and human growth hormone may have a role to play. No adverse effects of galactagogues were reported, but studies may not have been large enough to detect them, or they may not have been measured.

Three studies<sup>114,146,148</sup> of other interventions to enhance milk production were identified. These interventions are promising. A relaxation/imagery tape increased expressed milk volume without altering milk fat among mothers of recently born preterm infants. Breast massage increased the volumes of milk produced by mothers of recently born preterm infants using both simultaneous and sequential pumping, without altering fat content. Milk production was greater in mothers of non-breastfeeding preterm infants, including older preterm infants, after Therapeutic Touch (TT) than after mock TT or no treatment.

Cost-effectiveness outcomes were not reported in any of the seven studies.

### **Additional interventions to enhance breastmilk production: conclusions**

The evidence base overall is very limited. Very few data are available on breastfeeding outcomes either in the short or longer term; most outcomes measured were short-term measures of milk volume.

Pharmaceutical galactagogues seem to have little role to play: there is no evidence to support the use of oxytocin spray or metoclopramide. Further research is needed before domperidone and human growth hormone are used. None of the drugs is licensed for this purpose. There is some evidence to support the use of relaxation-related interventions, which may counter the stress-related lactation problems that women experience in neonatal units.<sup>197</sup>

Our search did not identify any studies investigating whether dietary customs or nutritional status of women in different ethnic groups and in different countries have any impact on breastmilk production. Participation of women from lower socioeconomic groups was limited, and there is no information available about the specific needs of mothers of twins and multiple births, who have increased needs for milk production.

As described above, enhancing breastmilk production is often a fundamentally important component of establishing and maintaining an adequate milk supply, especially when relying on milk expression before breastfeeding can be established. Milk expression is in itself a form of stimulating milk production, and these studies of additional interventions to enhance breastmilk production should not be viewed in isolation. Two studies<sup>114,144</sup> did have a concurrent protocol for expression, but both studies reported that mothers had problems with adhering to the frequency of expression recommended. Whether or not infants are breastfeeding is also a factor in breastmilk production, as is support; there is very limited evidence on these co-interventions from these studies. Another factor is likely to be close contact between mother and infant, which in itself can stimulate the hormones needed for milk production and release. No studies of milk production reported the use of skin-to-skin contact. These limitations are important in the light of the experience of clinical experts reported in Chapter 6, who indicated that a supportive environment,

and facilities for privacy and relaxation, were important for milk production.

Additional factors to consider in milk production also include the time since birth, as milk production is difficult to sustain over time, and the health and well-being of the mother.

Very sick mothers were unable to participate in these studies. Mothers of infants in neonatal units who are themselves critically ill are an important subgroup. In the light of concerns around their need to initiate and maintain a good breastmilk supply, they are likely to need specialised support for lactation, and issues related to excretion of drugs in breastmilk may need to be addressed. It is likely that infants of these mothers will need access to donor breastmilk at least at some stage in their care. In the case of mothers who are unable to communicate their wishes, for example, those who are unconscious or receiving respiratory support, prior knowledge of whether the mother intended to breastfeed would be valuable for staff. If women do indicate their feeding decision in pregnancy, noting the woman's views in her record would be helpful in these circumstances.

Important questions remain about ways of enhancing breastmilk production. From the evidence in this review, effective interventions are likely to be multifaceted. This is discussed in Chapter 9.

### **Interventions to support optimal nutritional intake from breastmilk**

This section examined interventions that aim to optimise the quality and/or quantity of the breastmilk fed to infants in neonatal units or following discharge. Three primary studies were identified;<sup>20,140,145</sup> only one rated as good quality. No studies reported primary outcomes of initiation of breastfeeding or oral feeding of expressed breastmilk.

One US study found that mothers of all educational levels demonstrated the ability accurately to measure the lipid content of their expressed breastmilk when taught.<sup>20</sup> Performing this procedure increased maternal satisfaction, and mothers felt they had influenced and made a difference to their infants' outcomes. Cost-effectiveness data were not reported though mothers taking responsibility for measuring lipid content of their expressed breastmilk may have the effect of reducing staff costs.

### **Optimal nutritional intake from breastmilk: conclusions**

Optimising the nutritional intake of infants in neonatal units and following discharge is a dominant concern in practice, yet there is virtually no evidence to inform effective ways of doing this for breastfed/breastmilk-fed infants. Preterm mothers' milk differs in composition from that of term mothers.<sup>86</sup> Optimising particularly the protein and lipid content of the milk is considered important to support growth, and, for this reason, fortification using artificial supplements has become a routine practice in many countries, although it has not been universally adopted in the UK. Enhancing the composition of mother's own milk offers an apparently simple solution to this problem. Good quality experimental evidence is, however, lacking to examine the effectiveness of this.<sup>198</sup>

### **Breastfeeding education and support interventions**

This section examined the provision of education and support for mothers of infants admitted to neonatal units. It included all forms of professional and peer education and support. Six primary studies<sup>117,126,143,152,153,166</sup> were identified. Two studies were rated as good quality<sup>117,126</sup> and three as moderate.<sup>143,153,166</sup>

All RCTs recruited women who wished to breastfeed. Merewood *et al.*<sup>143</sup> included a high proportion of mothers from low-income families; other studies appeared to recruit women from mixed socioeconomic backgrounds. Studies included both low birthweight and very low birthweight infants. Twins and multiples were included, but results were not reported separately.

There is good evidence that both hospital and community-based breastfeeding support from trained peer supporters in both industrialised and resource-poor settings improves breastfeeding outcomes, including in-hospital breastfeeding rates and a longer duration of breastfeeding and exclusive breastfeeding. Two study hospitals had Baby Friendly accreditation, suggesting that specific breastfeeding peer support for mothers in the community added effectiveness to standard Baby Friendly care, and one of these studies found that effectiveness was greater among the subgroup of African American participants.

In relation to hospital-based support from lactation consultants, one Canadian study found no effect,



but in this study of relatively affluent women both groups had access to other lactation consultants in the community and mothers reported that lactation consultants were their most used source of breastfeeding support. One US study found that professional lactation support in the neonatal unit resulted in more infants receiving their own mother's milk ever and at discharge.

No interventions to examine education for women or families on breastfeeding were identified.

### **Breastfeeding education and support interventions: conclusions**

Provision of skilled support, both peer and professional, in hospital and at home, is fundamentally important for mothers of term, healthy infants.<sup>199</sup> It is potentially more important for mothers facing the additional challenges associated with a preterm or low birthweight infant. The studies examined here provide strong evidence for the effectiveness of peer support for mothers of preterm and low birthweight infants who wish to breastfeed; such support enhanced the effectiveness of standard Baby Friendly care and increased effectiveness in African American women. There is also evidence for the effectiveness of professional support from lactation consultants in neonatal units. None of these studies was conducted in the UK.

The results of the health economics analysis (see Chapter 5) found that professional support was potentially cost-effective, which adds weight to the need to examine the implementation of this intervention in UK neonatal units. This is discussed in Chapters 8 and 9.

All three RCTs recruited women who wished to breastfeed. Sisk *et al.*<sup>106</sup> have reported that offering support to women who want to breastfeed was more effective than offering the same support to women who do not plan to breastfeed. The health economics analysis (see Chapter 5) found that the cost-effectiveness of professional support is increased if more women intend to breastfeed. As in other sections of this review, there are important implications for the promotion of breastfeeding in pregnancy.

The key contribution of specialist breastfeeding/breastmilk-feeding support for mothers of infants in neonatal units has been emphasised by the clinical expert subgroup (see Chapter 6), who indicated that both peer and professional support is crucial. They have indicated that not only do

women need support from a specialised member of staff to be available, but that all staff need to be trained to a minimum standard. This will be addressed in the next section.

The clinical experts subgroup (see Chapter 6) also indicated that an essential component of care for mothers of infants in neonatal units is evidence-based information on the importance of breastfeeding/feeding breastmilk for their infants, and on ways of enhancing this. Work is needed to examine information and education for mothers.

### **Staff training interventions**

This section examined interventions that aimed to enhance staff training in breastfeeding/breastmilk feeding in neonatal units. Two moderate-quality studies were identified, both from industrialised countries.<sup>81,149</sup> Both studies examined a multifaceted and multidisciplinary staff training programme for staff in neonatal units, both with self-study components.

Breastfeeding outcomes improved following the educational teaching package developed and implemented in the UK,<sup>81</sup> and also following a three-part intervention undertaken in the USA, which included a training component.<sup>149</sup> It is not possible to attribute these effects to individual components of these multifaceted interventions; it seems likely that the incremental effects of the different components all influenced breastfeeding rate.<sup>200</sup>

Other outcomes affected included an increase in skin-to-skin contact and improved test scores. One programme was reported to be well received by participating staff.

### **Staff training interventions: conclusions**

Lack of knowledge of breastfeeding/breastmilk feeding among health-care professionals is an important barrier to breastfeeding,<sup>78,79</sup> especially in the context of neonatal unit settings and the specialist skills needed. Parents report that some staff in the UK are underprepared for, and at times resistant to, the promotion of breastfeeding/breastmilk feeding for infants in neonatal units;<sup>46</sup> this includes some staff working in neonatal units, as well as midwifery, health visiting and medical staff in hospital and community settings. Neonatal unit staff themselves have recently reported that formula feeding is the norm in neonatal units, is easier, and indeed is necessary.<sup>201</sup> The limited evidence identified here suggests that educational

interventions delivered to a multidisciplinary staff group may increase health-care professionals' knowledge and can increase initiation rates and duration of breastfeeding, whether delivered alone or as part of a multifaceted intervention including maternal education and support.

The health economics analysis identified that staff training to provide supportive care was cost-effective (see Chapter 5), adding weight to the argument for implementing this in UK neonatal units.

Information from the clinical expert subgroup (see Chapter 6) indicates that educating all levels of staff on the neonatal unit is an essential component of changing practice. Their experience suggests that a dedicated specialist post is needed, but also that all staff need to be educated in the skills needed to support women and to promote breastfeeding/breastmilk intake for infants in neonatal units. It is unlikely that the effective interventions identified in other sections of this review will be implemented successfully in the absence of high-quality staff training.

Important questions remain about how to implement such training; these are addressed in Chapters 8 and 9.

### **Early hospital discharge with home support interventions**

This section examined the provision of early discharge followed by home support for infants from neonatal units. One moderate-quality study from New Zealand<sup>127</sup> was identified.

Early discharge with home support is not likely to have a positive effect, and may have an adverse effect, on duration rates of any and exclusive breastfeeding up to 6 months of age among clinically stable preterm infants. Readmission rates were found to remain unchanged or be slightly lower for the intervention group as a result of the early discharge intervention.<sup>127</sup> No outcomes related to cost-effectiveness of the early discharge and home support intervention were reported.

A high proportion of eligible mothers declined to participate and there were significantly more twins among the mothers who declined; the acceptability of early discharge for mothers may vary in different circumstances.

### **Early discharge with home support: conclusions**

The evidence base for the effectiveness and acceptability of early discharge with home support is very limited. Findings suggest that this intervention is unlikely to improve and may adversely affect the duration of breastfeeding although some benefits for infection rates and readmission rates to hospital may occur. Prolonged hospitalisation of preterm or low birthweight infants is associated with an increased risk of contracting infections, delays in mother–child bonding, higher costs<sup>155,161,202</sup> and adverse effects on family and functioning.<sup>203–205</sup>

Improved breastfeeding rates cannot be considered a justification for early discharge from UK neonatal units.

### **Organisation of care interventions**

No studies evaluating changes to the organisation of care between units, such as the introduction of a clinical network, met the inclusion criteria. One good-quality study<sup>137</sup> and one moderate-quality before/after study<sup>151</sup> examined organisation of care within a unit.<sup>138,151,154</sup> Both examined changes related to Baby Friendly accreditation of the associated maternity hospital.

Changes in the organisation of neonatal care driven by Baby Friendly accreditation of the host maternity hospital have significantly increased the numbers of infants receiving any breastmilk in the first week of enteral feeds, and the duration of any or exclusive breastfeeding prior to, and at, hospital discharge.<sup>137,151</sup> Both studies were conducted among infants of relatively lower risk within neonatal units. Mothers in one study were mostly black American and Hispanic women with typically low breastfeeding rates,<sup>137</sup> whereas the other study was conducted among Brazilian women with typically high breastfeeding rates.<sup>151</sup>

### **Organisation of care: conclusions**

The evidence base for organisation of care interventions is restricted to two before/after studies of Baby Friendly accreditation of the associated maternity hospital in industrialised countries, including relatively low-risk infants. These studies identified improvements in several breastfeeding-related outcomes as a result of this multifaceted intervention.

National data show that Baby Friendly accreditation of maternity hospitals is effective in increasing initiation among all women in the UK, including those from disadvantaged and vulnerable groups,<sup>80,206</sup> and limited data also support Baby Friendly accreditation in both the hospital and community<sup>207,208</sup> in both industrialised and resource-poor country settings. This intervention has been shown to be cost-effective.<sup>209</sup> As a consequence, implementation of the Baby Friendly Initiative as the minimum standard in NHS trusts has been recommended in two recent NICE guidelines.<sup>3,209</sup>

Several of the Ten Steps of the Baby Friendly Accreditation process may have a beneficial impact on neonatal units, and they inter-relate with much of the evidence presented in this review. These include:

- Step 1: Have a written breastfeeding policy that is routinely communicated to all health-care staff (see Chapter 6).
- Step 2: Train all health-care staff in the skills necessary to implement the breastfeeding policy (see in this chapter Breastfeeding education and support interventions).
- Step 3: Inform all pregnant women about the benefits and management of breastfeeding (see Chapter 6).
- Step 4: Help mothers initiate breastfeeding soon after birth (see Chapter 6; and in this chapter Expressing breastmilk interventions).
- Step 5: Show mothers how to breastfeed and how to maintain lactation even if they are separated from their infants (see Chapter 6; and in this chapter Expressing breastmilk interventions).
- Step 6: Give newborn infants no food or drink other than breastmilk, unless medically indicated.
- Step 7: Practice rooming-in, allowing mothers and infants to remain together 24 hours a day (see Chapter 6; and in this chapter Increased mother and infant contact interventions).
- Step 10: Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

However, additional steps, or modifications of the existing steps, are needed in the neonatal unit environment. Baby Friendly neonatal standards have been developed (see Appendix 11.1). The way in which these relate to the interventions examined in this review is discussed in Chapter

4 (see Organisation of care interventions) and in Appendix 11.2.

## Health economics and decision modelling: strengths, limitations and discussion

The economic model was developed with the aim of assessing the relative cost-effectiveness of interventions intended to promote/support breastfeeding in neonatal units. The model was developed with reference to the practices for decision modelling laid out in the Guidelines for Economic Evaluation in Health Technology Assessment.<sup>210</sup>

Details of the sources, methods and assumptions used in the analysis have been presented to ensure the transparency and enhance the understanding and interpretability of the study results. As with any modelling analysis, the structure is a simplification of reality, the purpose of which is to allow the synthesis of different types of data. In this instance, due to the complexity of the issue and a lack of available evidence, it was necessary to oversimplify the model structure. There was a lack of available evidence, particularly UK evidence, suggesting that the processes and decisions that are currently being made in the UK are not based on published research. While this lack of evidence is a major limitation to conducting any secondary research, it is hoped that the analysis undertaken will be useful in helping to direct future research and identify data limitations.

The data requirements of modelling are normally beyond the scope of the accompanying systematic review, which is often concerned with establishing effectiveness. Effectiveness data are necessary, but not sufficient, to facilitate modelling. This is because the model must encompass all consequences and costs that are related to the intervention under evaluation. The systematic review has identified a number of interventions that have a positive impact on breastfeeding rates and volumes of milk expressed. Additional literature searches identified very few economic studies, limited cost and resource use data, limited evidence on incidence of necrotising enterocolitis (NEC) and sepsis, and scant utility data. All of these are required in modelling. Few of the studies providing relevant data were UK studies. As a consequence, it was necessary to assume that the clinical data obtained from studies conducted in the USA and Europe were transferable to the UK

setting. In two of the studies providing effectiveness data for breastmilk on NEC and sepsis incidence, fortifier was added to mothers' milk, which is not routine practice in the UK. The impact of fortifier on outcomes is unclear.

Potentially, numerous benefits and disadvantages are associated with different forms of infant feeding, both for the mother and the infant. Some are well established, some are theoretical and it is likely that some are as yet unknown. It was necessary for the model to identify and focus on those clinical outcomes that would enable a link to breastfeeding/breastmilk to be established. Discussions with clinical advisors led us to devise a model that would evaluate the impact of breastfeeding/breastmilk on NEC and sepsis and in turn associated long-term health benefits. Limiting the clinical outcomes of interest may underestimate or overestimate the benefits of breastfeeding/breastmilk. Hopefully, what we have captured are those clinical outcomes that have the greatest health impact on these infants; maternal outcomes were not included. Interestingly, the identified literature showed little effect of mothers' milk consumption on sepsis, and it is likely that excluding sepsis from the analysis would have had limited impact on the results. Given the small number of outcomes incorporated it is extremely likely that several that might have impacted on the results have been excluded.

The evidence suggested that the intention of the mother regarding breastfeeding impacted on both initiation and duration of breastfeeding. Those mothers who had already decided to breastfeed their infant prior to entering hospital were more likely to express milk successfully for their infant. Intuitively, this would suggest that promotion of breastfeeding should occur at an early stage of pregnancy to reinforce lactation support in hospital.

Guidelines suggest that the time horizon of the model applied should be long enough to capture all relevant costs and benefit differences between the interventions.<sup>211</sup>

In order to capture the costs and health benefits over the lifetime of the infants, it was assumed that the disability state of the infant once diagnosed would remain constant for the lifetime of the child. Each disability state incurred an annual cost, which was multiplied by the life expectancy to obtain a lifetime cost for each disability. These were then incorporated into the model. As costs and benefits

were incurred over a lifetime, discounting was conducted. Data limitations meant that it was necessary to ignore readmission costs and the additional treatment costs that may be incurred. While this may lead to an underestimation of the costs, the relative difference between the two interventions is likely to remain the same. Additionally, given that the other potential health benefits and protective benefits of breastmilk have not been incorporated into the model, it is possible that the readmission and treatment rates would be higher in the formula-fed population, hence increasing the costs incurred in the normal staff contact arm. Further, no negative health effects of consumption of mothers' milk were modelled. No adverse effects of breastfeeding were incorporated into the model and no searches were conducted to identify any. However, of those clinical papers that did inform the model none reported adverse effects from breastfeeding.

As has already been mentioned, the available evidence regarding resource use and costing for the UK setting was extremely poor. Despite conducting additional searches it was necessary to use national cost data at an aggregate level. This led to a number of different scenarios being evaluated in the sensitivity analysis. The reference costs indicated a number of resources that had already been included in the unit (daily) cost. To avoid double counting it was considered that all costs incurred in an inpatient day had been captured. However, surgical costs, which were explicitly stated to have been excluded from the unit cost, were included.

The inclusion of formula and breast pump provision in the hotel costs of an inpatient stay does not capture the incremental effect of the intervention on formula consumption and breast pump use. Due to uncertainty regarding the current practice of provision of breast pumps in the UK, it was difficult to measure and cost changes in breast pump use. However, various scenarios with formula costs, donor milk costs, expression kit costs and length of stay were evaluated in an attempt to ascertain the impact of these resource changes on the cost-effectiveness results. The results show that any variations in resources have an impact on the incremental cost-effectiveness ratio (ICER), particularly the introduction of donor milk, and this is to be expected. However, without a more detailed costing study, it is impossible to ascertain whether the actual resources that would be used in a real-life situation are reflected in the analysis outcomes.

Further, the costing of milk banking was problematic given the current situation in the UK. While donor milk is available in some units, it is not the norm. The report from the Donor Milk Working Group (2003) demonstrated that provision of regionally or nationally organised milk banking facilities could reduce the cost per litre and allow all preterm infants the opportunity to receive donor human milk rather than preterm formula. To demonstrate the impact of achieving the lower cost, two separate modelling scenarios were presented. The higher cost of donor milk did impact on the results and, while the two lower birthweight groups remained cost-effective options, the 1750–2500 g population obtained an ICER greater than the £20,000 threshold. However, donor milk would become cost-effective if the mechanisms by which it is provided were improved.

The enhanced staff contact intervention, which provided additional trained professional support in hospital, was more effective and less costly (due to reduced neonatal illness) than normal staff contact in most sensitivity analysis scenarios, and it is instructive to ask what, if anything, could prevent enhanced staff support from being cost-effective. In the sensitivity analyses, there were four data inputs that had more than a marginal impact on the cost-effectiveness of enhanced staff contact. These were: increasing the cost of the staff contact; reducing the length of stay in the units by half; including the cost of expression kits; and reducing the effect size of mothers' milk relative to formula on incidence of confirmed NEC. Only the last had a major effect on the cost-effectiveness, and it was only important for the heaviest birthweight population.

The primary reason that enhanced staff contact is cost-effective in the model is that it is relatively cheap. The model assumes that other requirements for milk expression are already in place in neonatal units. The BLISS report<sup>46</sup> and clinical advisors to this study suggest that private rooms for expressing milk should be provided, and that there are overnight rooms in some units, so it is possible that no extra facility costs need be incurred. However, this is uncertain. But what this analysis demonstrates is that by increasing the number of infants receiving breastmilk there would be a reduction in the severity and incidence of illness.

Overall, the outcomes of the model are fairly robust to the changes in the parameters varied

in sensitivity analysis. We have made no attempt to address structural uncertainty and we are aware that the model structure may be too basic. In conclusion, the results demonstrate the likely cost-effectiveness of enhanced staff contact. However, we acknowledge that further research is required to describe fully the many other aspects of breastfeeding that could influence effectiveness. We hope that the model we have developed will contribute to future work in this field.

## Conclusions

This review has identified effective and cost-effective interventions, few, if any, of which are widely practised in UK neonatal units. Limitations of the effectiveness review include the scarcity of high-quality evidence identified for most types of intervention, the heterogeneity of interventions and settings studied, and the fact that most studies examined predominantly clinically stable infants. Limitations of the economic analysis are similar, in that little existing evidence was identified. Although there are preliminary indications that enhanced staff contact may be cost-effective, further evidence is required to provide results with confidence.

We used the Advisory Group and clinical expert subgroup to inform the topic area, and study methodology and priorities for future research. It is possible that bias was introduced as a consequence. To address this, we have been both cautious and transparent in our use of information gained in this way.

Before considering implications for policy, practice and future research, it is important to note that one fundamentally important finding of this review, described in several sections and emphasised by the clinical expert subgroup in Chapter 6, is that many interventions inter-relate. It seems unlikely that specific clinical interventions such as double pumping or cup feeding will be effective if used alone, and particularly in the absence of staff training or of an environment in which mothers are encouraged and supported in having close and ongoing contact with their infants, and to breastfeed/express breastmilk. These issues are addressed in Chapters 8 and 9.



## Chapter 8

# Implications for policy, practice and education

Implications for policy, practice and education are presented here using the Ottawa Charter for health promotion,<sup>101</sup> which we have used as a conceptual framework [see Chapter 3, Data handling process (p. 13)]. We first examined the findings of this study, then consulted with the Advisory Group and clinical expert subgroup to agree conclusions and recommendations as follows.

### Public policy and public health

No studies related to public policy were identified. Although increasing breastfeeding initiation and duration rates for the population as a whole is a national policy priority, the profile of this vulnerable group of mothers and infants needs to be raised in relation to public health policy. Such a change could be accomplished by overtly including this group in the national targets for initiation and duration of breastfeeding, and recognising the contribution that breastfeeding/feeding with breastmilk could make to addressing inequalities in health and specifically to meeting Public Service Agreement targets on health inequalities and infant mortality. Other policy issues should be considered to enable breastfeeding/breastmilk feeding for these mothers and infants, including employment and financial protection for women whose infants require lengthy hospital stays and ongoing care at home, and the provision of support at home for mothers with other children.

The extensive changes needed to create sustained improvement in neonatal units will be difficult to implement with the current shortage of trained staff. The effectiveness and cost-effectiveness of staff support demonstrated in this study could encourage service commissioners to increase staffing levels in neonatal units and to promote staff training, as staff training and support for mothers is relatively inexpensive compared with the resources needed for neonatal care (see Chapter 4, Breastfeeding education and support interventions (p. 48); see also Chapter 5).

Interventions were more effective in women who wanted to breastfeed. This implies that

antenatal interventions that increase initiation of breastfeeding among all women and families<sup>3,59</sup> should be implemented or strengthened to increase the numbers of women who intend to breastfeed, including those who give birth prematurely [see Chapter 4: Increased mother and infant contact interventions (p. 19); Expressing breastmilk interventions (p. 34); Breastfeeding education and support interventions (p. 48)]. This includes support for the Baby Friendly Initiative as the minimum standard in NHS Trusts [see Chapter 4: Organisation of care interventions (p. 59)].

Facilities should be available for the safe transport, storage and feeding of breastmilk including own mother's milk and donor milk [see Chapter 4: Expressing breastmilk interventions (p. 34); Chapter 5: Methods for health economics modelling (p. 63)]. The milk bank system in the UK is locally organised and neither uniformly available nor adequately monitored, leaving infants vulnerable to gaps in provision.<sup>91</sup> Donor milk banking is currently being reviewed by NICE and changes should await the outcome of that review ([www.nice.org.uk/guidance/index.jsp?action=byID&o=11973](http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11973)).

To inform policy developments and clinical care, improved monitoring is needed [see Chapter 4: Increased mother and infant contact interventions (p. 19); see also Chapter 5]. Consistent national data are currently lacking on disease and length of stay, individual infant treatment pathways and resource use for infants starting life in neonatal units in the UK; these data should be routinely collected. There is a need to develop consensus definitions of the initiation and duration of breastfeeding/breastmilk feeding with specific reference to infants admitted to neonatal units and their mothers. This should record both the stage at which the infant initially receives breastmilk and the stage at which nutritive breastfeeding is attained, as well as noting whether or not women initiated breastmilk expression. In addition, routine recording of breastfeeding/breastmilk feeding status at the point of hospital discharge and subsequently would aid comparison with breastfeeding rates for the general population.

A national infrastructure should be established to allow consistent records to be kept and collated in a manner that allows data analysis. Furthermore, feeding, health, educational, social and costs outcomes beyond discharge from neonatal unit care, for example from paediatric wards, hospital readmissions, GP and health visitor care, need to be incorporated. This is consistent with the Every Child Matters<sup>58</sup> monitoring framework. Given the potential of standard and newly introduced feeding methods to impact on safety and on breastfeeding, exclusivity and duration of breastfeeding/breastmilk feeding and health outcomes should be monitored routinely for these infants. This should include details of breastfeeding/breastmilk feeding and supplemental feeding including both content and methods of feeding, using standardised and validated measurements.

We have proposed definitions [see Chapter 9: General issues of methodology and design (p. 108)] relevant to initiation and duration of breastfeeding/breastmilk feeding for infants who start life in neonatal units and their mothers.

ChiMat, the new national Child and Maternal Health Observatory, has an important role to play in identifying gaps in existing data and reporting systems; driving improvements in data and supporting implementation of improved systems for data collection and reporting; developing new indicators to support measurement and monitoring in relation to child and maternal health policy areas; and tackling health inequalities. These recommendations are relevant to that work programme.

## Supportive environments

The views of parents should be fundamental to the organisation of care in neonatal units, and arrangements should be in place to ascertain and respond to those on a regular basis (see Chapter 6).

Avoiding non-essential separation of mothers and infants and offering all possible opportunities for engagement of the mother in caregiving for her infant should be priorities for care. Some neonatal units provide 'transitional care' areas in which the mother can be accommodated together with her clinically stable infant from about 32 weeks of gestation. The clinical expert subgroup noted that provision of such care is far from uniform, and this needs to be addressed [see Chapter 4: Increased mother and infant contact interventions (p. 19);

Expressing breastmilk interventions (p. 34); see also Chapter 6].

This evidence base warrants increased implementation of a minimum of 1–2 hours daily kangaroo skin-to-skin contact for clinically stable infants of low and very low birthweight and their mothers. Core components of this intervention include kangaroo skin-to-skin contact during the hospital stay combined with personal breastfeeding education and support from a skilled neonatal nurse to assist mothers with initial breastfeeding experiences, recognition of subtle infant feeding cues and encouragement of self-regulated feeding in response to these cues. Routine implementation of early discharge as a component of kangaroo mother care is not supported [see Chapter 4: Increased mother and infant contact interventions (p. 19)].

Frequent effective expression of breastmilk is fundamentally important. Clean, comfortable, private facilities with appropriate breast pumps and equipment for pumping and for milk storage, should be freely available for mothers. In the absence of national guidance, mothers' breastmilk should be handled in accordance with local guidelines approved by infection control specialists;<sup>212</sup> national guidance would support local units in developing appropriate policies, and should be considered. Specialised support should be given to the mother wherever she is in the hospital, including the postnatal ward, transitional care, ICU, delivery suite or another specialist unit such as a mental health unit, and at home to encourage her to maximise her milk output. Mothers of twins and multiples are likely to require additional care and skilled support [see Chapter 4: Expressing breastmilk interventions (p. 34); see also Chapter 6].

There is evidence that a range of supportive/relaxation measures can help to enhance milk volume without reducing fat content. Mothers of infants who wish to initiate or maintain breastmilk production should be offered the opportunity for relaxation before and during expression. This will include facilities for expressing either away from the normal stresses of the neonatal unit or close to their infants, as preferred by the mother [see Chapter 4: Expressing breastmilk interventions (p. 34); Additional interventions to enhance breastmilk production (p. 40)].

The current system for the organisation of neonatal care can result in parents being at some distance



from their infant(s). Support, including practical and financial support, is needed for the mother to visit frequently, and to express breastmilk both in hospital and home environments [see Chapter 4: Increased mother and infant contact interventions (p. 19); Expressing breastmilk interventions (p. 34); see also Chapter 6].

Enabling mothers and infants to have close and ongoing contact is likely to require changes to the built environment in neonatal units. Consideration of this should be part of the planning process for the design of all new neonatal units.

## Community action

Hospital- and community-based peer support from women who have themselves had an infant in a neonatal unit and who are trained in breastfeeding counselling should be considered for all women with infants in neonatal units and following discharge. Suitable remuneration and standards of training and supervision will be required, with special consideration of the complex physical and social needs of mothers of infants who have started life in neonatal units [see Chapter 4: Breastfeeding education and support interventions (p. 48)].

## Development of personal and professional skills

Trained professional breastfeeding support in the neonatal unit should be offered to all mothers, particularly those who are ill. This intervention has been shown to be clinically and potentially cost-effective [see Chapter 4: Breastfeeding education and support interventions (p. 48); see also Chapter 5].

Double pumping with a hospital-grade electric pump with suitable silastic inserts and well-fitting flanges to prevent injury to mothers has advantages over other methods in the first 2 weeks, and support should be available to enable mothers to do this. However, once the mother is discharged home, she may benefit from using other methods such as a hand-operated pump, or hand expression, for milk removal at home, as well as continuing to use the hospital pump when she is in hospital. Mothers should be encouraged to try a range of pumps at this stage to identify which works best for each individual. Mothers should be taught how to hand express, for use in circumstances where a pump is not available or

not working [see Chapter 4: Expressing breastmilk interventions (p. 34)].

There is very limited evidence to support the use of prescribed medication to stimulate or maintain production. The use of such substances may divert attention from more fundamental aspects of care unless seen as an adjunct to other forms of supportive care [see Chapter 4: Additional interventions to enhance breastmilk production (p. 40)].

Mothers can be taught to separate foremilk and hindmilk accurately. Where this technique is used as part of infant care on the neonatal unit, this could support mothers' involvement in the care of their infants [see Chapter 4: Interventions to support optimal nutritional intake from breastmilk (p. 46)].

Our interpretation of the limited but important evidence is that cup feeding can be used in neonatal units as an alternative to bottle feeding for clinically stable infants who are ready for oral feeds, but only in settings where staff are adequately trained and mothers wish to use it. Important questions remain about its use and more widespread adoption should await future research. Until such evidence is available, parents' views should be respected, all equipment used should be appropriate to the developmental stage of the infant, care should be taken to optimise nutritional intake, staff should be adequately trained, and care taken to support the early transition to breastfeeding [see Chapter 4: Interim feeding methods and related interventions (p. 28)].

There is no evidence to support the removal of pacifier use in infants who are not able to suck feed, as non-nutritive sucking remains an important issue.<sup>213</sup> There is inadequate evidence to support the use of caregivers' fingers in place of pacifiers, and this should be recognised as an intervention in its own right that should be fully tested before adoption into practice [see Chapter 4: Interim feeding methods and related interventions (p. 28)].

## Reorientation of health services

All clinical experts reported that positive change requires strong and informed leadership within the neonatal unit. Planned change, engaging all professional groups, was reported as essential. The

motivation for change was perceived as likely to be increased by knowledge and understanding of the evidence about health risks associated with formula feeding. An evidence-based policy for all staff was seen as essential, with audit of compliance and outcomes (see Chapter 6).

There is an urgent need to enhance the training of all staff working with families in neonatal units and following discharge in the skills needed to promote and protect breastfeeding, and support breastfeeding women. This should be covered during specialty training, and be seen as an aspect of continuing professional development. The design and delivery of training should be shared between trusts, universities, royal colleges and professional bodies, and the UNICEF Baby Friendly programme, and could include support from the NHS Institute for Innovation and Improvement [see Chapter 4: Increased mother and infant contact interventions (p. 19); Interim feeding methods and related interventions (p. 28); Expressing breastmilk interventions (p. 34); Additional interventions to enhance breastmilk production (p. 40); Breastfeeding education

and support interventions (p. 48); Staff training interventions (p. 55); see also Chapters 5 and 6].

Communication between staff caring for the mother and infant in all settings in hospital, staff in community settings, and the mother and her family needs to be improved in order to maximise the mother's milk production and increase her opportunity to be with her infant [see Chapter 4: Increased mother and infant contact interventions (p. 19); Interim feeding methods and related interventions (p. 28); Expressing breastmilk interventions (p. 34); Additional interventions to enhance breastmilk production (p. 40); Breastfeeding education and support interventions (p. 48); Staff training interventions (p. 55); see also Chapters 5 and 6].

The limited but relatively good quality of the evidence base for Baby Friendly accreditation further supports the existing evidence-based action<sup>59</sup> and guidance<sup>3</sup> for implementation of the UNICEF UK Baby Friendly Initiative for maternity services as the minimum standard in England and Wales [see Chapter 4: Organisation of care interventions (p. 59)].

## Chapter 9

# Research agenda

We formulated research questions arising from the current evidence base, and identified gaps in the evidence using the Ottawa Charter for Health Promotion<sup>101</sup> as a framework. We then consulted with the Advisory Group and the clinical expert subgroup to agree on priorities. The list of priority research questions has resulted from this process. The methodological issues identified here should be considered in the design of all future research to improve the quality and relevance of studies.

### Methodological issues

Conducting research with mothers and infants in neonatal units is complex and challenging. The inevitable distress experienced by parents complicates the process of information and consent, and the fragility of the infants requires the highest possible standards of care. Nevertheless there are studies in this review that have succeeded in conducting research to very high standards.

Some of the methodological problems identified in the existing evidence base are common in health-related research. Studies did not always report the details of interventions, standard care or characteristics of participants. Some results were not reported in ways that enabled checks on the quality of analysis. Compliance was a problem even in some studies of otherwise good quality. Many studies were too small to yield conclusive results. Outcomes measured tended to be short-term indicators such as milk intake or time to discharge. Longer-term breastfeeding, health, development and psychosocial outcomes were seldom, if ever, measured. Very few randomised controlled trials (RCTs) were identified, even in topic areas where this is a feasible approach. Of the six RCTs conducted in the UK, only two were assessed as good quality; both were related to milk production and expression. This has limited the confidence with which recommendations can be made, especially for changes to clinical practice.

Other problems were specific to the field being studied. Breastfeeding and breastmilk feeding

behaviour was varied and seldom reported in detail. 'Breastfeeding' can describe both partial and exclusive feeding, and feeding with breastmilk as well as feeding from the breast. Infants may receive supplements of formula or other products, which are not standard across time, countries or hospitals. There is wide variation in the composition and use of artificial 'fortifiers', and, despite a lack of evidence informing their appropriate use, they are so widely accepted that their use is not always reported. Expressed breastmilk can vary in amount and composition; fresh or stored mothers' milk differs from donor milk, which may be derived from one or more mothers at different stages of lactation and treated in different ways before being used. Methods of feed administration (bottle, tube or cup) were seldom reported in detail yet may differentially affect outcomes. Because formula feeding and bottle feeding have been widespread for so long in the UK, breastfeeding and breastmilk feeding and the techniques required to support them may be novel, and staff are likely to be unfamiliar with them.

### Gaps in the evidence base: Ottawa Charter Framework

The evidence base is very limited, and it is especially limited in regard to the UK, both in quantity and in quality. In the two areas where evidence is strongest, increased mother–infant contact and support, only one UK study has been conducted and that was over 20 years ago.<sup>147</sup> Of the eight UK studies included in this review, only two were rated as good quality.<sup>125,144</sup> For many interventions, the main evidence was derived from US studies (20, 42% overall). This limits the transferability of findings and indicates the lack of investment to date in research in this field in the UK.

The gaps in the evidence base for each of the five health promotion categories of the Ottawa Charter Framework are summarised in *Table 25* and discussed in the following section.

TABLE 25 Gaps in the evidence base: Ottawa Charter Framework

Areas of health promotion action (Ottawa Charter)	Evidence of effectiveness for interventions to promote and support breastfeeding in neonatal units
<i>Public policy</i> – e.g. legislation, fiscal measures, inclusion in public health targets	No studies identified
<i>Supportive environments</i> (which protect natural resources and generate healthy living and working conditions) – e.g. public attitude and infrastructure to support breastfeeding for newborns in hospital (not separating mothers and infants, private room to express, etc.) or at home (equipment, home visits, etc.)	Increased mother and infant contact via kangaroo skin-to-skin contact Early discharge with home support No studies identified on privacy or other aspects of humane care
<i>Community action</i> – e.g. self-help and social support through family, peer or other community support	Peer support No studies identified on family or other community support
<i>Development of personal skills</i> – e.g. education programmes, clinical support	Education and counselling Limited evidence for: <ul style="list-style-type: none"> <li>• methods of enhancing milk supply</li> <li>• methods of interim feeding</li> <li>• methods of expressing breastmilk</li> <li>• mothers' measurement of breastmilk quality</li> </ul>
<i>Reorientation of health services</i> – e.g. managed clinical networks, breastfeeding policy, Baby Friendly Initiative, training of staff, transport service	Baby Friendly Initiative Protocol-based care Staff training and education No studies identified examining effects of managed clinical networks or transport services

## Public policy and public health

No studies specifically related to public policy and public health either in the UK or internationally were identified. No studies of cost-effectiveness that could inform service commissioning were identified. Moreover, we had difficulty obtaining relevant data to populate the economic models developed. This indicates an urgent need to collect more routine data on infant feeding, growth and nutrition processes and outcomes in neonatal care.

An important finding of this review is that interventions, including skin-to-skin contact, expression and support, appeared to be more effective, and enhanced staff contact was more cost-effective, in women who wanted to breastfeed. The implication of this is that public health/health promotion interventions that increase initiation rates in the population may have an important part to play in raising rates among this group of mothers and infants.

Very few studies included mothers from subgroups with specific needs, who are over-represented in families with infants in neonatal units. This includes families from low-income backgrounds, minority ethnic and cultural groups, teenage

and unsupported mothers, mothers using non-prescription drugs and other illegal substances, and mothers with serious illness including those requiring prescription drugs. For no studies were these subgroups a central concern, meaning that no studies were adequately powered to examine these issues.

Twelve studies reported that twins and multiples were included; all other studies did not report this or indicated that multiples were specifically excluded. Only one study<sup>125</sup> reported any results separately for singletons and multiples, limiting the conclusions that can be drawn. No study examined twins and multiples and their mothers as a central concern, so all were underpowered in this regard. The needs of twins and multiples and their mothers are especially important in areas such as milk expression and mother–infant contact where having more than one infant presents specific challenges.

No studies examined the effect of marketing breastmilk substitutes on families of a preterm infant, nor on the attitudes and practices of staff caring for them.

## Supportive environments

No studies examined ways to enhance breastfeeding/breastmilk feeding for mothers and infants in situations where they are separated by distance or by illness of the mother. Similarly no studies explored the effects on breastfeeding of the facilities that were provided. Relevant features of a supportive environment could include mechanisms to enable mothers to be with their infants, including assistance with transport; also a welcoming, private, comfortable, quiet environment for parents, and specifically one for mothers to express milk, to talk with staff, to consider bad news about their infant's progress, and to talk with other parents. Clinical experts considered this to be very important (see Chapter 6), and an example of a resource designed for and by mothers has been identified.<sup>21</sup> It could be argued that empirical study of this issue is unnecessary since such facilities should be available as standard care, as a matter of human dignity and rights. In practice, however, it is reported that such facilities are not available in the UK,<sup>43,46</sup> and it is feasible that cost-effectiveness data could contribute to provision of such an environment in the financially restricted environment of the NHS.

Similarly, no studies examined the effect on breastfeeding of broader aspects of humane care or of developmental care, where the environment of the whole neonatal unit offers quiet, supportive and developmentally appropriate facilities such as day-night lighting, appropriate handling, and close contact between mothers and infants. Kangaroo skin-to-skin contact is an important component of such care.

There were no studies of the impact of the provision of a comprehensive, quality-controlled, affordable milk bank service on breastfeeding/breastmilk and health outcomes.

## Community action

Studies of peer support in the community were identified. None was conducted in the UK, however, and results require validation in UK settings, especially in regard to provision for women on low incomes, or with complex health and social needs, in urban or rural settings, and from different ethnic groups.

No studies of social support for these families were identified; this may be particularly important for mothers of multiples and for mothers with other children.

Only one study<sup>109</sup> was identified that examined the involvement of fathers or other family members in education and/or support for breastfeeding.

## Development of personal and professional skills

The majority of the studies identified included only clinically stable infants. Only one study reported outcomes separately for a specific group of infants (very low birthweight).<sup>140</sup> Little can be said about the skills needed to care for these particularly vulnerable mothers and infants. Developmentally appropriate interventions for infants of different gestational age or weight have not been examined in robust studies.

No studies specifically examined the ability of caregivers to assess and respond to infant cues on the coordination of sucking, swallowing and breathing to support oral feeding and transition to the breast.

Very few studies examined maternal complications such as painful nipples and breasts, engorgement, mastitis, problems with positioning and attachment, insufficient milk; mothers' views and experiences (e.g. Fewtrell *et al.*, 2001<sup>125</sup>); or measures of physical or emotional well-being such as exhaustion or depression. Only one study indicated that participating women had significant health problems,<sup>144</sup> despite the fact that mothers of infants in neonatal units are themselves more likely to be ill. Breastfeeding/breastmilk feeding is demanding and difficult for mothers of infants in neonatal units, and maternal health and well-being is essential to its success. Skills to address some of these problems have been identified for mothers of term, healthy infants,<sup>3,59</sup> and the specific care needed to help mothers of preterm and low birthweight infants needs to be examined. Maternal outcomes should be included in future research studies.

No studies of staff training used principles of adult learning or psychological models to underpin their approach. Behaviour change is challenging, and work is needed to identify theoretical approaches that might work to sustain such change.

No studies examined the current routine protocols for assessing weight and growth for infants in neonatal units and following discharge. The clinical expert subgroup noted that without an understanding of lactation and breastfeeding, or a supportive environment for lactating mothers,

such protocols can have a negative impact on breastfeeding/breastmilk feeding. Ways of assessing infant growth, weight and development without undermining lactation and while also promoting breastmilk intake and breastfeeding should be examined.

No studies were identified in which infants in neonatal units had particular problems in feeding from the breast, such as cleft lip and palate, although studies involving infants in other settings have been conducted that may be relevant (e.g. Glenny *et al.*, 2004;<sup>214</sup> Darzi *et al.*, 1996<sup>215</sup>).

## Reorientation of health services

Very little research has been conducted on the current organisation of neonatal units, especially interunit care, clinical networks and transport, in particular to examine ways of using transport and effective links between units within a clinical network to reduce mother–infant separation and increase fathers' contact time and involvement, particularly for families in rural settings or reliant on public transport.

Included studies did not examine the contribution the health service could make for mothers and infants from deprived groups or groups where breastfeeding rates were very low.

## Recommendations for research

### General issues of methodology and research design

Future trials should adhere to appropriate standards of reporting, for example the CONSORT statement for clinical trials ([www.consort-statement.org/index.aspx?o=1030](http://www.consort-statement.org/index.aspx?o=1030)), and all trials should be registered from the start with the International Standard Randomised Controlled Trial Number Register ([www.controlled-trials.com/isrctn](http://www.controlled-trials.com/isrctn)).

Research designs should incorporate an understanding of lactation and breastfeeding, and should develop standardised measures of breastfeeding and breastmilk feeding, including measurement of dose and exposure period and noting both the content and mode of feeding. Suggested standardised measures are as follows:

- *Initiation of breastmilk feeding for infant* When the infant receives first dose of breastmilk from any source by any method. Whether mother's own or donor milk (or both) should be recorded, as

should the method of feeding – breastfeeding, or expressed milk by bottle, cup or tube.

- *Initiation of breastmilk expression* When the mother starts to express breastmilk by any method.
- *Initiation of breastfeeding* When the mother provides the first nutritive feed directly from the breast.
- *Duration of breastfeeding/breastmilk feeding* Any and exclusive intake of breastmilk from any source by any method; measured at weekly intervals until and including hospital discharge. Whether mother's own or donor milk (or both) should be recorded, as should the method of feeding – breastfeeding, or expressed milk by bottle, cup or tube.

It will also be important to use standardised measures of intake of formula and fortifier, to include information about the amount and timing of feeds taken, the type of formula and fortifier used, and mode of feeding (i.e. bottle, tube, cup).

Future studies should provide clear sampling frames for target population groups including a priori sample size calculations and comparability of participants regarding demographic, socioeconomic and clinical characteristics at the points of enrolment and randomisation into comparison groups. Clear descriptions of 'standard care' (the comparator), admission and discharge policies, the nature of the intervention and standards of competence achieved by staff or peer supporters are critical to adapting interventions or replicating them in other settings.

Future studies should involve from the outset parents who have experienced the neonatal unit environment, and take account of the views of expert clinical staff in all relevant disciplines.

Experimental designs should also take into consideration the fact that it is rarely possible to conduct a single intervention; a recurring issue in this study has been the potential for confounding and the likelihood of a Hawthorne effect arising through associated change in parental and staff attitudes and practice. For many questions it will be more appropriate to randomise units rather than individual mothers or infants, as in the large RCT of Baby Friendly accreditation conducted by Kramer *et al.* (2001),<sup>4</sup> or to conduct high-quality before/after studies in one or several units.

Although outcomes in the infants will usually be of primary interest we note a need for more information on other aspects such as maternal

health and well-being, parents' views and experiences, and staff views and behaviour. Outcomes in the infant may include short-, medium- and long-term measures of feeding, health and development. We observed a particular dearth of measurements of medium- or long-term outcomes, and psychosocial outcomes. Data to inform better cost-effectiveness research would be particularly valuable.

Studies should examine the specific needs and care for women with different feeding intentions and from different socioeconomic and ethnic backgrounds, and should include sick mothers, mothers of very low birthweight and very preterm infants, and mothers of multiple births and their infants. There is also likely to be a need either to stratify by birthweight at the randomisation stage or to explore the very different needs of infants at different gestational ages and birthweights, and their families, by subgroup analysis.

Where interventions may lead to differential feeding outcomes, for example exclusive or partial intake of breastmilk, it is important that research designs build in measurement of short-, medium- and long-term health outcomes. Such designs offer an unbiased opportunity to explore the effects of maternal milk provision on health and disease outcomes, as in Kramer *et al.*;<sup>4</sup> this information can otherwise be difficult to acquire.

## Recommendations for future research studies

Research recommendations are grouped in the following categories:

- Work to be considered when planning all future studies.
- Urgent preliminary work to inform best practice for future intervention studies.
- Recommended studies:
  - priority level 1: intervention studies to address urgent gaps
  - priority level 2: specific interventions and staff training.

### **Work to be considered when planning all future studies**

#### **Examining health and development outcomes and costs**

Studies that examine the dose–response relationship between feeding and health and development outcomes would inform cost-effectiveness issues, which influence service commissioning decisions. Long-term studies are

necessary to quantify more precisely the short-, medium- and long-term costs associated with not breastfeeding related to maternal and infant health and infant and child development. Resource use should be evaluated in any study of health and development outcomes to ensure that cost data applicable to the specific population can be obtained. This is true for both the long-term cost of treating disability and the cost of disease in neonatal units, especially NEC.

Such work could be conducted in the context of existing or planned cohort studies, or could be incorporated into large RCTs (such as those proposed below), or could use data available from routine monitoring, were an appropriate national system to be established. A large prospective cohort of 600 very low birthweight infants born to racially and economically diverse mothers has recently been funded by the National Institutes of Health (NIH) in the USA (Principal Investigator Dr Paula Meier). This study will examine health outcomes, health service issues and cost-effectiveness of different methods of infant feeding. Future research in this field should take this study into consideration. UK studies are required to determine the resource use and costs of disease and treatment in the UK.

Future modelling work should focus on capturing the multiple episodes of disease, adverse effects, complications at various intervals throughout the infant's stay in the neonatal unit, and the impact of the history of these events on the long-term quality of life of the infant. Data for this type of model were not available at the time of this study. In addition, utilities and health outcomes for mothers related to infant feeding should be measured; although the health and development outcomes for infants are important, the outcomes for mothers should not be overlooked.<sup>216</sup>

This work on outcomes should inform and support, and be incorporated in, large experimental studies such as those outlined below.

#### **Parents' health, views, experiences and needs**

Within the context of each of the studies described below, nested qualitative and quantitative research should be conducted to examine a range of issues including the health and well-being of the mother, the infant feeding decisions and experiences of mothers of infants in neonatal units; the views and experiences of fathers and other family members and their role in infant feeding decisions; the educational needs of mothers and fathers

to promote breastfeeding/breastmilk feeding; the feeding-related needs of parents of infants with specific challenges, including multiple births, extremely low birthweight and congenital anomalies; and the diverse needs of parents from different population subgroups.

**Urgent preliminary work to inform best practice for future intervention studies**

It is evident from the studies reviewed that an important contributor to the findings is the compliance or lack of compliance of staff and of women with the novel intervention. It is also evident that interventions to be tested in future studies are not in common practice in UK settings. Before best practice intervention studies can be conducted in accordance with the principles of the Medical Research Council (MRC) guidelines on testing complex interventions,<sup>217</sup> the following pilot/preliminary studies are urgently needed.

**Staff training**

A staff training programme should be developed and tested to equip staff with the necessary knowledge, commitment and behaviour change to support appropriate and effective expressing of breastmilk, kangaroo skin-to-skin contact and access to peer support. This should address the needs of medical, neonatal nursing, midwifery, health visiting, speech therapy and related staff. The design of this programme should use psychological models of change and principles of adult learning (e.g. refs 218,219). A qualitative study on staff decision-making in neonatal units related to breastfeeding in Scotland has recently been completed, and these results will be relevant to inform study design (Dr Rhona McInnes, University of Stirling, personal communication, 2008).

**Mother–infant contact**

Adequate evaluation of kangaroo skin-to-skin contact in the UK would benefit from increased understanding of the views of staff and parents, improved staff training, and provision of facilities that enable mothers to remain with their infants. Qualitative research is needed to inform the development of a best practice model consistent with that practised in some units in Sweden, the USA and Colombia (e.g. ref. 220). This work also needs to reach consensus on the parameters of infant clinical stability within which kangaroo skin-to-skin contact can be used safely.

A pilot experimental evaluation of a best-practice model of kangaroo skin-to-skin contact

could then be conducted in the UK. This could use a prospective before/after study design, to examine the impact of best-practice kangaroo skin-to-skin contact on breastfeeding and health outcomes among clinically stable infants of any gestational age. The evaluation should include core components of staff training and attitude and behaviour change, equipment, facilities, and staff and parental views as well as detailed description of the intervention components for potential replication or adaptation. Participants should include mothers and families from a range of ethnic and socioeconomic backgrounds and feeding intentions.

**Peer support**

Provision of peer support for mothers in neonatal units is complicated by the diversity of their problems and by the relatively high proportion who have complex health and social needs. The introduction of peer support into neonatal care will require qualitative research to examine the needs and wishes of mothers and their families, the views of hospital and community staff, and a workload analysis. This would inform the training of peer supporters and the design of an intervention study.

Together the qualitative research and the experimental evaluation would provide the necessary basis to inform the design of future intervention studies.

**Recommended studies**

**Priority level 1: intervention studies to address urgent gaps**

Based on the preliminary work described above, the following intervention studies are important priorities to address gaps in the current evidence base.

**Kangaroo skin-to-skin contact for clinically less stable and very preterm infants and their mothers**

The evidence base on kangaroo skin-to-skin contact is limited to clinically stable infants. An RCT of kangaroo skin-to-skin contact for infants who are clinically less stable, possibly very preterm infants, has not been conducted in any country. Such a study would address the current evidence gap around the impact of this simple intervention in these particularly vulnerable mothers and infants. The design should take into consideration the methodological recommendations above.

**Supportive environment and staff training**

It is evident that multifaceted interventions are required to create sustained change. The main



elements of the intervention to be tested in this study would be: a breastfeeding promotion policy and associated implementation programme with identified leadership; skilled professional care and support; information and education for women; kangaroo skin-to-skin contact; facilities to enable initiation and maintenance of breastmilk production; care to enhance self-regulatory feeding; and community-based care following discharge. These elements are very similar to the Baby Friendly neonatal standards. Measuring their effectiveness and cost-effectiveness would be the aim of this study. The control group would receive standard care. Such a study would have significant training and resource implications, and would require the development work outlined above before it could be designed and implemented. Possible designs to be considered include a cluster RCT, or a high-quality before/after study. Measurement of short-, medium- and long-term feeding and health outcomes and resource use in the context of this study as recommended above would greatly contribute to the understanding of the contribution feeding has to make to the health and well-being of these infants and their mothers, and to cost-effectiveness, as demonstrated by Kramer *et al.*<sup>4</sup>

#### **Peer support intervention study**

The impact of peer support for mothers and families of infants in the neonatal unit has not been tested in the UK. It could be a more cost-effective intervention than professional support, and has the potential of offering consistent support across both hospital and community settings. Based on the preliminary research outlined above, a large RCT of peer support offered to mothers in both hospital and community settings could be designed, to include short-, medium- and longer-term breastfeeding/breastmilk feeding outcomes, infant health and well-being, women's views and experiences, staff views, utilities and costs.

#### **Priority level 2: specific interventions and staff training**

##### ***Initiating and sustaining milk production: intervention studies***

In addition to inclusion of this aspect in the multifaceted supportive environment study, studies are needed to examine ways of maximising milk production. These studies would be smaller in scale and could be conducted over a shorter timescale than the large multifaceted study. Such studies should include examination of different pumps and pumping regimens, and the use of co-interventions of skin-to-skin contact, additional support, and

relaxation. They should be informed by current understanding of the physiology of lactation and the specific physiological challenges for mothers who give birth preterm.

There is no evidence that pharmaceutical galactagogues are effective when used in isolation from supportive measures; studies that do not include provision of skilled lactation support for all participants should not be conducted. Where studies of galactagogues are conducted, they should examine their differential effectiveness in different subgroups (e.g. women separated from their infants for long periods, women with problems in producing adequate milk even when well supported and expressing frequently), and include a wide range of breastfeeding/breastmilk outcomes and assess women's views.

##### ***Interim feeding methods and related interventions: intervention studies***

High-quality research is needed to explore the appropriate mechanisms for feeding infants who are unable to breastfeed, both clinically stable and less stable ones, as there are problems associated with both bottle feeding and cup feeding. This requires an adequately sized RCT of bottle versus cup feeding, in which the bottles, teats and cups used are appropriate for the infant's developmental stage. Outcomes should include short- and long-term measures of infant growth and health; and also breastfeeding/breastmilk feeding outcomes, including exclusivity, support needed post discharge to move from cup/bottle to breastfeeding, costs, utilities, and the views of parents and staff. This work should be conducted in an environment where early transition to the breast is encouraged by close contact between mother and infant and where staff are skilled in both techniques.

RCTs are needed to examine both short-term and longer-term outcomes of the use of nipple shields and other feeding aids for mothers of infants who are in neonatal units and have positioning and attachment problems, including infants with specific feeding challenges such as cleft lip and palate. These trials should be conducted in an environment in which the feeding aids are introduced to mothers by staff trained and experienced in breastfeeding, where ongoing support is available, and where the discontinuation of use of the feeding aids is also supported. Longer-term impact and any problems experienced by the mothers should be examined. Physiological research on milk transfer during feeding with and without shields would inform ways

of enabling early transition to breastfeeding in this population.

***Enhancing nutritional composition of human milk***

Evidence is lacking on the effectiveness and safety of techniques to enhance the nutritional composition of human milk including commercial fortifiers and the use of components of human milk. In the light of the important short-, medium- and long-term health and development outcomes related to this question, high quality research is required.

***Baby Friendly accreditation of maternity services***

Further good-quality research is required to evaluate the effect of Baby Friendly accreditation of maternity services on infants who are in neonatal units and have very low birthweight, gestational age of < 30 weeks and/or are small for gestational age. Good-quality concurrent evaluations should also be conducted to validate the existing evidence related

to breastfeeding outcomes among all infants in neonatal units, and including preterm and low birthweight infants cared for in transitional care units and postnatal wards, in UK settings.

***Promoting behaviour change, staff education and training***

Research is needed to examine the most efficient and effective ways of promoting behaviour change and of conducting staff training – at continuing professional development level, to improve the knowledge and skills of current staff; and at preregistration/specialty training level, to ensure all new staff are educated in essential skills. Studies should examine staff attitudes and beliefs, barriers to change and strategies to support the implementation of change in stressful circumstances; there are examples of such work (e.g. ref. 221). This work will be informed by the preliminary work on staff training described above.



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### Contribution of authors

Mary J Renfrew led this study and contributed to the concept and design, analysis and interpretation of data, drafting of the report and final approval of the version to be published.

Dawn Craig led the health economics component of the study and contributed to the concept and design, analysis and interpretation of data, drafting

of the report and final approval of the version to be published.

Lisa Dyson contributed to the concept and design, analysis and interpretation of data, drafting of the report and final approval of the version to be published.

Felicia McCormick contributed to the concept and design, analysis and interpretation of data, drafting of the report and final approval of the version to be published.

Stephen JC Rice contributed to the concept and design, analysis and interpretation of data, drafting of the report and final approval of the version to be published.

Sarah King contributed to the concept and design, revising the report critically for important intellectual content and final approval of the version to be published.

Kate Misso contributed to the design of searches of the literature for evidence and references management, revising the report critically for important intellectual content and final approval of the version to be published.

Elizabeth Stenhouse contributed to the concept and design, revising the report critically for important intellectual content and final approval of the version to be published.

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# Appendix I

## Members of the research team, advisory group, and clinical expert subgroup

### Research team

Dawn Craig, Research Fellow in Health Economics, Centre for Reviews and Dissemination, University of York

Lisa Dyson (from January 2008), Senior Researcher, Mother and Infant Research Unit, University of York

Sarah King (until December 2007), Senior Researcher, Mother and Infant Research Unit, University of York

Felicia McCormick, Research Fellow, Mother and Infant Research Unit, University of York

Kate Misso, Information Officer, Centre for Reviews and Dissemination, University of York

Mary Renfrew (Principal Investigator), Professor of Mother and Infant Health, Director, Mother and Infant Research Unit, University of York

Stephen Rice, Research Fellow in Health Economics, Centre for Reviews and Dissemination, University of York

Elizabeth Stenhouse, Senior Lecturer in Midwifery Research, University of Plymouth

Tony Williams, Reader in Child Nutrition and Consultant in Neonatal Paediatrics, St George's, University of London

### Advisory Group members

Gene Anderson, Edward J. and Louise Mellen Professor Emerita of Nursing, Case Western Reserve University; Professor Emerita, University of Florida

Rosie Dodds, Policy Researcher, National Childbirth Trust: service user/consumer representative member (Chair)

Sandra Lang, Consultant in Infant and Young Child Feeding and Newborn Care, Senior Teaching

Fellow, Centre for International Health and Development, University College London Institute of Child Health, London

Shelley Mason, Family Support Co-ordinator, BLISS

Paula Meier, Professor and Director for Clinical Research and Lactation, Neonatal Intensive Care Unit, Rush University Medical Center, Chicago

Josephine Patterson, Breastfeeding Advisor, Winnicott Baby Unit, St Mary's Hospital, Paddington

Mark Sculpher, Professor of Health Economics, University of York

Sarah O'Sullivan, Service user/consumer member

Amanda Sowden, Associate Director, Centre for Reviews and Dissemination, University of York

Louise Wallace, Professor and Director, Health Behaviour and Health Service Management Interventions programmes, Health and Lifestyles Interventions Research Centre, Coventry University

### Clinical Expert Subgroup

Victoria Dugbartey, Infant Feeding Specialist, Queen Charlotte's and Chelsea Hospital, London

Kerstin Hedberg Nyqvist, Department of Women's and Children's Health, Uppsala University

Elizabeth Jones, Infant Feeding Advisor, University Hospital of North Staffordshire

Caroline King, Paediatric Clinical Lead, Hammersmith Hospital, and Honorary Lecturer, Imperial College, London

Camilla Kingdon, Consultant Neonatologist, Queen Charlotte's and Chelsea Hospital, London



# Appendix 2

## Search strategies

### Appendix 2.1: Effectiveness review

#### 1. Search strategy to identify systematic reviews

##### MEDLINE and MEDLINE In-Process Citations (OVID)

1. Breast Feeding/
2. breastfe\$.ti,ab.
3. (breast\$ adj2 (fed\$ or feed\$)).ti,ab.
4. Lactation/ or Milk, Human/
5. (breastmilk\$ or lactat\$).ti,ab.
6. (transitional care and (maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies)).ti,ab.
7. ((breast\$ or mother\$ or human or maternal\$) adj2 milk).ti,ab.
8. (nursing adj2 (maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies)).ti,ab.
9. ((maintain\$ or maintenance\$ or establish\$ or begin\$ or start\$ or commenc\$ continu\$ or sustain\$ or prolong\$ or extend\$) adj2 (milk or breast\$ fed\$ or breast feed\$ or lactat\$ or nursing or suck\$ or breastfed\$ or breastfeed\$)).ti,ab.
10. ((milk or breastmilk) adj2 (donor\$ or donat\$ or bank\$)).ti,ab.
11. ((milk or breast\$) adj2 express\$).ti,ab.
12. (breast pump\$ or breastpump\$).ti,ab.
13. (hand\$ adj2 express\$).ti,ab.
14. kangaroo.ti,ab.
15. ((skin\$ adj2 contact) or skin-to-skin).ti,ab.
16. (suck\$ adj2 breast\$).ti,ab.
17. (tube adj2 (feed or fee\$)).ti,ab.
18. (cup adj2 (fed or fee\$)).ti,ab.
19. (bottle adj2 (fed or fee\$)).ti,ab.
20. (transition adj2 breast\$).ti,ab.
21. Lactation Disorders/nu, di, dh, pc, dt, th [Nursing, Diagnosis, Diet Therapy, Prevention & Control, Drug Therapy, Therapy]
22. Galactorrhea/di, dh, nu, pc, dt, th
23. (Galactagogue\$ or Galactogogue\$ or lactagogue\$ or lactogogue\$ or caffeine or hops or fenugreek or fennel seed\$ or blessed thistle or domperidone or alfalfa).ti,ab.
24. Caffeine/tu [Therapeutic Use]
25. Humulus/ or Plants, Medicinal/tu or Metoclopramide/tu or Sulpiride/tu or Plant Extracts/tu or Chlorpromazine/tu or Dopamine Antagonists/tu or Oxytocin/tu or Thyrotropin-Releasing Hormone/tu or Human Growth Hormone/tu
26. Trigonella/ or (Sulpiride or metoclopramide or domeperidone or chlorpromazine or oxytocin or dopamine antagonist\$ or thyrotropine releasing hormone\$ or TRH or human growth hormone\$).ti,ab.
27. Foeniculum/ or creamatocrit\$.ti,ab.
28. Cnicus/
29. Domperidone/tu [Therapeutic Use]
30. Medicago sativa/
31. (nipple\$ shield\$ or breast\$ shield\$).ti,ab.
32. (dropper\$ adj2 (fed or fee\$)).ti,ab.
33. (spoon adj2 (fed or fee\$)).ti,ab.
34. (syringe\$ adj2 (fed or fee\$)).ti,ab.
35. supplementer\$.ti,ab.
36. Pacifiers/
37. (pacifier\$ or dummy or dummies or soother\$).ti,ab.
38. (non-nutritive suck\$ or nonnutritive suck\$).ti,ab.
39. Rooming-in Care/
40. (rooming-in or room-in or co-sleep\$).ti,ab.
41. (bedshar\$ or bed-shar\$).ti,ab.
42. ((bedside\$ or bed side\$) adj2 (cot or cots or cradle\$ or crib or crib)).ti,ab.
43. or/1-42
44. Intensive Care Units, Neonatal/
45. Intensive Care, Neonatal/
46. (nicu or nicus).ti,ab.
47. (scbu or scbus).ti,ab.
48. ((special or intensive or icu\$) adj3 (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies)).mp.
49. ((newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies) adj2 unit\$).mp.
50. or/44-49

51. 43 and 50
52. Health Promotion/
53. (promotion\$ or promoting).ti,ab.
54. promot\$.ti,ab.
55. Inservice Training/
56. ((staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$) adj2 training).ti,ab.
57. social support/
58. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 support\$).ti,ab.
59. (antenatal educat\$ or ante natal educat\$ or neonatal educat\$ or neo natal educat\$ or prenatal educat\$ or pre natal educat\$ or preconception\$ educat\$ or pre conception\$ educat\$).ti,ab.
60. (postpartum educat\$ or post partum educat\$ or postnatal educat\$ or post natal educat\$).ti,ab.
61. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 involv\$).ti,ab.
62. (early adj2 discharge\$).ti,ab.
63. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 attitude\$).ti,ab.
64. ((staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$) adj2 attitude\$).ti,ab.
65. Patient Education/
66. ((peer\$ or social\$ or interpersonal\$ or inter personal\$ or midwife\$ or midwife\$ or profession\$ or practitioner\$ or nursing or lactation) adj2 (encourag\$ or motivat\$ or support\$ or guid\$ or counsel\$ or consult\$ or advic\$ or advis\$)).ti,ab.
67. (lactation adj2 (consultant\$ or expert\$ or adviser\$ or specialist\$ or advisor\$)).ti,ab.
68. (humane adj2 (prematu\$ or pre matur\$ or premie or premies or perinat\$ or perinat\$ or neonat\$ or neo nat\$) adj1 care).ti,ab.
69. ((tallin or Levin) adj1 (method\$ or approach\$ or program\$ or propos\$ or unit\$)).ti,ab.
70. ((mother\$ or parent\$ or maternal\$ or famil\$) adj1 (led or focus\$ or lead\$ or direct\$ or center\$ or centre\$) adj2 care).ti,ab.
71. (abm or lll or bfi or bfhi or nct).ti,ab.
72. (association of breastfeeding mothers or association of breast feeding mothers).ti,ab.
73. (la leche league or national childbirth trust).ti,ab.
74. (baby friendly or breaststart or breast start or beststart or best start or nidcap).ti,ab.
75. (support\$ strateg\$ or support\$ system\$ or support\$ program\$).ti,ab.
76. (Neonat\$ Individuali?ed Developmental Care and Assessment Program\$).ti,ab.
77. (Newborn\$ Individuali?ed Developmental Care and Assessment Program\$).ti,ab.
78. or/52-77
79. 50 and 78
80. 51 or 79
81. animal/
82. human/
83. 81 not (81 and 82)
84. 80 not 83
85. 84 not (letter or comment or editorial).pt.
86. (200708\$ or 200709\$ or 200710\$ or 200711\$ or 200712\$).ed.
87. 2008\$.ed.
88. 86 or 87
89. 85 and 88
90. review.ab.
91. review.pt.
92. meta-analysis.ab.
93. meta-analysis.pt.
94. meta-analysis.ti.
95. or/90-94
96. 89 and 95

## 2. Search strategy to identify primary studies

### MEDLINE and MEDLINE In-Process Citations (OVID)

1. Breast Feeding/ (18587)
2. breastfe\$.ti,ab. (7049)
3. (breast\$ adj2 (fed\$ or feed\$)).ti,ab. (11128)
4. Lactation/ or Milk, Human/ (37074)
5. (breastmilk\$ or lactat\$).ti,ab. (85491)
6. (transitional care and (maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo nat\$ or perinat\$ or perinat\$ or premie or premies)).ti,ab. (22)
7. ((breast\$ or mother\$ or human or maternal\$) adj2 milk).ti,ab. (12479)
8. (nursing adj2 (maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo nat\$ or perinat\$ or perinat\$ or premie or premies)).ti,ab. (1852)
9. ((maintain\$ or maintenance\$ or establish\$ or begin\$ or start\$ or commenc\$ continu\$ or sustain\$ or prolong\$ or extend\$) adj2 (milk or breast\$ fed\$ or breast feed\$ or lactat\$ or nursing or suck\$ or breastfed\$ or

- breastfeed\$).ti,ab. (2789)
10. ((milk or breastmilk) adj2 (donor\$ or donat\$ or bank\$)).ti,ab. (400)
  11. ((milk or breast\$) adj2 express\$).ti,ab. (2623)
  12. (breast pump\$ or breastpump\$).ti,ab. (159)
  13. (hand\$ adj2 express\$).ti,ab. (888)
  14. kangaroo.ti,ab. (1019)
  15. ((skin\$ adj2 contact) or skin-to-skin).ti,ab. (1046)
  16. (suck\$ adj2 breast\$).ti,ab. (44)
  17. (tube adj2 (feed or fee\$)).ti,ab. (3468)
  18. (cup adj2 (fed or fee\$)).ti,ab. (33)
  19. (bottle adj2 (fed or fee\$)).ti,ab. (1537)
  20. (transition adj2 breast\$).ti,ab. (27)
  21. Lactation Disorders/nu, di, dh, pc, dt, th [Nursing, Diagnosis, Diet Therapy, Prevention & Control, Drug Therapy, Therapy] (627)
  22. Galactorrhea/di, dh, nu, pc, dt, th (429)
  23. (Galactagogue\$ or caffeine or hops or fenugreek or fennel seed\$ or blessed thistle or domperidone or alfalfa).ti,ab. (22466)
  24. Caffeine/tu [Therapeutic Use] (836)
  25. Humulus/ or Plants, Medicinal/tu or Metoclopramide/tu or Sulpiride/tu or Plant Extracts/tu or Chlorpromazine/tu or Dopamine Antagonists/tu or Oxytocin/tu or Thyrotropin-Releasing Hormone/tu or Human Growth Hormone/tu (19226)
  26. Trigonella/ or (Sulpride or metoclopramide or domperidone or chlorpromazine or oxytocin or dopamine antagonist\$ or thyrotropine releasing hormone\$ or TRH or human growth hormone\$).ti,ab. (44536)
  27. Foeniculum/ or creamatocrit\$.ti,ab. (86)
  28. Cnicus/ (0)
  29. Domperidone/tu [Therapeutic Use] (306)
  30. Medicago sativa/ (2584)
  31. (nipple\$ shield\$ or breast\$ shield\$).ti,ab. (59)
  32. (dropper\$ adj2 (fed or fee\$)).ti,ab. (2)
  33. (spoon adj2 (fed or fee\$)).ti,ab. (39)
  34. (syringe\$ adj2 (fed or fee\$)).ti,ab. (12)
  35. supplementer\$.ti,ab. (5)
  36. Pacifiers/ (136)
  37. (pacifier\$ or dummy or dummies or soother\$).ti,ab. (3052)
  38. (non-nutritive suck\$ or nonnutritive suck\$).ti,ab. (217)
  39. Rooming-in Care/ (348)
  40. (rooming-in or room-in or co-sleep\$).ti,ab. (1572)
  41. (bedshar\$ or bed-shar\$).ti,ab. (191)
  42. ((bedside\$ or bed side\$) adj2 (cot or cots or cradle\$ or crib or crib)).ti,ab. (0)
  43. or/1-42 (219727)
  44. Intensive Care Units, Neonatal/ (5994)
  45. Intensive Care, Neonatal/ (2696)
  46. (nicu or nicus).ti,ab. (2642)
  47. (scbu or scbus).ti,ab. (71)
  48. ((special or intensive or icu\$) adj3 (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies)).mp. (13714)
  49. ((newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies) adj2 unit\$).mp. (7994)
  50. or/44-49 (15629)
  51. 43 and 50 (908)
  52. Health Promotion/ (29989)
  53. (promotion\$ or promoting).ti,ab. (82762)
  54. promot\$.ti,ab. (329719)
  55. Inservice Training/ (13078)
  56. ((staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$) adj2 training).ti,ab. (7232)
  57. social support/ (29285)
  58. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 support\$).ti,ab. (6551)
  59. (antenatal educat\$ or ante natal educat\$ or neonatal educat\$ or neo natal educat\$ or prenatal educat\$ or pre natal educat\$ or preconception\$ educat\$ or pre conception\$ educat\$).ti,ab. (210)
  60. (postpartum educat\$ or post partum educat\$ or postnatal educat\$ or post natal educat\$).ti,ab. (30)
  61. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 involv\$).ti,ab. (4806)
  62. (early adj2 discharge\$).ti,ab. (1901)
  63. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 attitude\$).ti,ab. (2157)
  64. ((staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$) adj2 attitude\$).ti,ab. (4195)
  65. Patient Education/ (48363)
  66. ((peer\$ or social\$ or interpersonal\$ or inter personal\$ or midwife\$ or midwife\$ or profession\$ or practitioner\$ or nursing or lactation) adj2 (encourag\$ or motivat\$ or support\$ or guid\$ or counsel\$ or consult\$ or advic\$ or advis\$)).ti,ab. (21378)

67. (lactation adj2 (consultant\$ or expert\$ or adviser\$ or specialist\$ or advisor\$)).ti,ab. (168)
68. (humane adj2 (prematu\$ or pre matur\$ or premie or premies or perinat\$ or perinat\$ or neonat\$ or neo nat\$) adj1 care).ti,ab. (6)
69. ((tallin or Levin) adj1 (method\$ or approach\$ or program\$ or propos\$ or unit\$)).ti,ab. (2)
70. ((mother\$ or parent\$ or maternal\$ or famil\$) adj1 (led or focus\$ or lead\$ or direct\$ or center\$ or centre\$) adj2 care).ti,ab. (601)
71. (abm or lll or bfi or bfhi or nct).ti,ab. (1267)
72. (association of breastfeeding mothers or association of breast feeding mothers).ti,ab. (0)
73. (la leche league or national childbirth trust).ti,ab. (53)
74. (baby friendly or breaststart or breast start or beststart or best start or nidcap).ti,ab. (323)
75. (support\$ strateg\$ or support\$ system\$ or support\$ program\$).ti,ab. (7123)
76. (Neonat\$ Individuali?ed Developmental Care and Assessment Program\$).ti,ab. (14)
77. (Newborn\$ Individuali?ed Developmental Care and Assessment Program\$).ti,ab. (23)
78. or/52-77 (471619)
79. 50 and 78 (963)
80. 51 or 79 (1702)
81. animal/ (4116476)
82. human/ (9822139)
83. 81 not (81 and 82) (3119775)
84. 80 not 83 (1691)
85. 84 not (letter or comment or editorial).pt. (1651)
86. (200607\$ or 200608\$ or 200609\$ or 200610\$ or 200611\$ or 200612\$).ed. (339554)
87. 2007\$.ed. (400072)
88. 86 or 87 (739626)
89. 85 and 88 (133)
90. review.ab. (343906)
91. review.pt. (1295130)
92. meta-analysis.ab. (12712)
93. meta-analysis.pt. (15848)
94. meta-analysis.ti. (8155)
95. or/90-94 (1453608)
96. 89 and 95 (32)
97. Breast Feeding/ (18587)
98. breastfe\$.ti,ab. (7049)
99. (breast\$ adj2 (fed\$ or feed\$)).ti,ab. (11128)
100. Lactation/ or Milk, Human/ (37074)
101. (breastmilk\$ or lactat\$).ti,ab. (85491)
102. (transitional care and (maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo nat\$ or perinat\$ or perinat\$ or premie or premies)).ti,ab. (22)
103. ((breast\$ or mother\$ or human or maternal\$) adj2 milk).ti,ab. (12479)
104. (nursing adj2 (maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo nat\$ or perinat\$ or perinat\$ or premie or premies)).ti,ab. (1852)
105. ((maintain\$ or maintenance\$ or establish\$ or begin\$ or start\$ or commenc\$ continu\$ or sustain\$ or prolong\$ or extend\$) adj2 (milk or breast\$ fed\$ or breast feed\$ or lactat\$ or nursing or suck\$ or breastfed\$ or breastfeed\$)).ti,ab. (2789)
106. ((milk or breastmilk) adj2 (donor\$ or donat\$ or bank\$)).ti,ab. (400)
107. ((milk or breast\$) adj2 express\$).ti,ab. (2623)
108. (breast pump\$ or breastpump\$).ti,ab. (159)
109. (hand\$ adj2 express\$).ti,ab. (888)
110. kangaroo.ti,ab. (1019)
111. ((skin\$ adj2 contact) or skin-to-skin).ti,ab. (1046)
112. (suck\$ adj2 breast\$).ti,ab. (44)
113. (tube adj2 (feed or fee\$)).ti,ab. (3468)
114. (cup adj2 (fed or fee\$)).ti,ab. (33)
115. (bottle adj2 (fed or fee\$)).ti,ab. (1537)
116. (transition adj2 breast\$).ti,ab. (27)
117. Lactation Disorders/nu, di, dh, pc, dt, th [Nursing, Diagnosis, Diet Therapy, Prevention & Control, Drug Therapy, Therapy] (627)
118. Galactorrhoea/di, dh, nu, pc, dt, th (429)
119. (Galactagogue\$ or caffeine or hops or fenugreek or fennel seed\$ or blessed thistle or domperidone or alfalfa).ti,ab. (22466)
120. Caffeine/tu [Therapeutic Use] (836)
121. Humulus/ or Plants, Medicinal/tu or Metoclopramide/tu or Sulpiride/tu or Plant Extracts/tu or Chlorpromazine/tu or Dopamine Antagonists/tu or Oxytocin/tu or Thyrotropin-Releasing Hormone/tu or Human Growth Hormone/tu (19226)
122. Trigonella/ or (Sulpride or metoclopramide or domperidone or chlorpromazine or oxytocin or dopamine

- antagonist\$ or thyrotropine releasing hormone\$ or TRH or human growth hormone\$.ti,ab. (44536)
123. Foeniculum/ or creatatocrit\$.ti,ab. (86)
124. Cnicus/ (0)
125. Domperidone/tu [Therapeutic Use] (306)
126. Medicago sativa/ (2584)
127. (nipple\$ shield\$ or breast\$ shield\$.ti,ab. (59)
128. (dropper\$ adj2 (fed or fee\$)).ti,ab. (2)
129. (spoon adj2 (fed or fee\$)).ti,ab. (39)
130. (syringe\$ adj2 (fed or fee\$)).ti,ab. (12)
131. supplementer\$.ti,ab. (5)
132. Pacifiers/ (136)
133. (pacifier\$ or dummy or dummies or soother\$.ti,ab. (3052)
134. (non-nutritive suck\$ or nonnutritive suck\$.ti,ab. (217)
135. Rooming-in Care/ (348)
136. (rooming-in or room-in or co-sleep\$.ti,ab. (1572)
137. (bedshar\$ or bed-shar\$.ti,ab. (191)
138. ((bedside\$ or bed side\$) adj2 (cot or cots or cradle\$ or crib or crib)).ti,ab. (0)
139. or/97-138 (219727)
140. Intensive Care Units, Neonatal/ (5994)
141. Intensive Care, Neonatal/ (2696)
142. (nicu or nicus).ti,ab. (2642)
143. (scbu or scbus).ti,ab. (71)
144. ((special or intensive or icu\$) adj3 (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies)).mp. (13714)
145. ((newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies) adj2 unit\$.mp. (7994)
146. or/140-145 (15629)
147. 139 and 146 (908)
148. Health Promotion/ (29989)
149. (promotion\$ or promoting).ti,ab. (82762)
150. promot\$.ti,ab. (329719)
151. Inservice Training/ (13078)
152. ((staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$) adj2 training).ti,ab. (7232)
153. social support/ (29285)
154. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 support\$.ti,ab. (6551)
155. (antenatal educat\$ or ante natal educat\$ or neonatal educat\$ or neo natal educat\$ or prenatal educat\$ or pre natal educat\$ or preconception\$ educat\$ or pre conception\$ educat\$.ti,ab. (210)
156. (postpartum educat\$ or post partum educat\$ or postnatal educat\$ or post natal educat\$.ti,ab. (30)
157. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 involv\$.ti,ab. (4806)
158. (early adj2 discharge\$.ti,ab. (1901)
159. ((family or families or parent\$ or mother\$ or father\$ or partner\$) adj2 attitude\$.ti,ab. (2157)
160. ((staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$) adj2 attitude\$.ti,ab. (4195)
161. Patient Education/ (48363)
162. ((peer\$ or social\$ or interpersonal\$ or inter personal\$ or midwife\$ or midwife\$ or profession\$ or practitioner\$ or nursing or lactation) adj2 (encourag\$ or motivat\$ or support\$ or guid\$ or counsel\$ or consult\$ or advic\$ or advis\$)).ti,ab. (21378)
163. (lactation adj2 (consultant\$ or expert\$ or adviser\$ or specialist\$ or advisor\$)).ti,ab. (168)
164. (humane adj2 (prematu\$ or pre matur\$ or premie or premies or perinat\$ or peri nat\$ or neonat\$ or neo nat\$) adj1 care).ti,ab. (6)
165. ((tallin or Levin) adj1 (method\$ or approach\$ or program\$ or propos\$ or unit\$)).ti,ab. (2)
166. ((mother\$ or parent\$ or maternal\$ or famil\$) adj1 (led or focus\$ or lead\$ or direct\$ or center\$ or centre\$) adj2 care).ti,ab. (601)
167. (abm or lll or bfi or bfhi or nct).ti,ab. (1267)
168. (association of breastfeeding mothers or association of breast feeding mothers).ti,ab. (0)
169. (la leche league or national childbirth trust).ti,ab. (53)
170. (baby friendly or breaststart or breast start or beststart or best start or nidcap).ti,ab. (323)
171. (support\$ strateg\$ or support\$ system\$ or support\$ program\$.ti,ab. (7123)
172. (Neonat\$ Individuali?ed Developmental Care and Assessment Program\$.ti,ab. (14)
173. (Newborn\$ Individuali?ed Developmental Care and Assessment Program\$.ti,ab. (23)
174. or/148-173 (471619)
175. 146 and 174 (963)
176. 147 or 175 (1702)

177. animal/ (4116476)
178. human/ (9822139)
179. 177 not (177 and 178) (3119775)
180. 176 not 179 (1691)
181. 180 not (letter or comment or editorial).  
pt. (1651)

### 3. Search strategy to identify primary studies evaluating galactagogues

#### MEDLINE and MEDLINE In-Process Citations (OVID)

1. Caffeine/tu [Therapeutic Use]
2. Humulus/ or Plants, Medicinal/tu or Metoclopramide/tu or Sulpiride/tu or Plant Extracts/tu or Chlorpromazine/tu or Dopamine Antagonists/tu or Oxytocin/tu or Thyrotropin-Releasing Hormone/tu or Human Growth Hormone/tu
3. Trigonella/ or (Sulpiride or metoclopramide or domperidone or chlorpromazine or oxytocin or dopamine antagonist\$ or thyrotropine releasing hormone\$ or TRH or human growth hormone\$).ti,ab.
4. Foeniculum/
5. Cnicus/
6. Domperidone/tu [Therapeutic Use]
7. Medicago sativa/
8. Lactation Disorders/dh, dt
9. Galactorrhea/dh, dt
10. (Galactagogue\$ or Galactogogue\$ or lactagogue\$ or lactogogue\$ or caffeine or hops or fenugreek or fennel seed\$ or blessed thistle or domperidone or alfalfa).ti,ab.
11. Metoclopramide/tu [Therapeutic Use]
12. Growth Hormone/tu [Therapeutic Use]
13. (maxalon or dolmatil or motilium or syntocinon or Sulpiride or metoclopramide or domperidone or chlorpromazine or oxytocin or dopamine antagonist\$ or thyrotropine releasing hormone\$ or TRH or human growth hormone\$).ti,ab.
14. or/1-13
15. Infant, Premature/
16. (premie or premies or pre term\$ or preterm\$ or prematur\$).mp.
17. 15 or 16
18. 14 and 17
19. limit 18 to yr='1991 - 2008'

## Appendix 2.2: Health economics review

### Searches of health economics resources

#### NHS Economic Evaluation Database (NHS EED) (internal CRD B system)

The NHS EED search was from inception up to 8 August 2007 and identified 38 references.

#### Limit e

1. S breastfe\$ or breastmilk\$ or lactat\$
2. S breast\$(w2)fed\$ or breast\$(w2)feed\$
3. S transitional(w)care and (maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1)nat\$ or premie or premies)
4. S (breast\$ or mother\$ or human or maternal\$(w)milk
5. S nursing(w)(maternal\$ or mother\$ or baby or babies or infant\$ or newborn\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1)nat\$ or premie or premies)
6. S (maintain\$ or maintenance\$ or establish\$ or begin\$ or start\$ or commenc\$ continu\$ or sustain\$ or prolong\$ or extend\$(w)(milk or breast\$(w1)fed\$ or breast(w1)feed\$ or lactat\$ or nursing or suck\$ or breastfed\$ or breastfeed\$)
7. S (milk or breastmilk)(w)(donor\$ or donat\$ or bank\$)
8. S (milk or breast\$(w)express\$
9. S breast(w1)pump\$ or breastpump\$
10. S hand\$(w)express\$
11. S kangaroo or (skin\$(w2)contact) or suck\$(w)breast\$
12. tube(w)(feed or fee\$)
13. S cup(w)(fed or fee\$)
14. S bottle(w)(fed or fee\$)
15. S transition(w)breast\$
16. S lactagogue\$ or lactogogue\$ or Galactagogue\$ or caffeine or hops or fenugreek or (fennel(w1)seed\$) or (blessed(w1)thistle) or domperidone or alfalfa
17. S Sulpiride or metoclopramide or domperidone or chlorpromazine or oxytocin or (dopamine(w)antagonist\$) or (thyrotropine(w)releasing(w)hormone\$) or TRH or (human(w)growth(w)hormone\$) or creatatocrit\$
18. S (nipple\$(w)shield\$) or (breast\$(w)shield\$)
19. S (dropper\$(w)fed\$) or (dropper\$(w)fee\$)
20. S (spoon(w)fee\$) or (spoon(w)fed\$)



21. S (syringe\$(w)fed\$) or (syringe\$(w)fee\$)
22. s supplementer\$ or pacifier\$ or dummy or dummies or soother\$
23. (non-nutritive(w)suck\$) or (nonnutritive(w)suck\$)
24. s rooming(w1)in or room(w1)in or co(w1)sleep\$ or bedshar\$ or bed(w1)shar\$
25. s bedside\$(w)(cot or cots or cradle\$ or crib or crib)
26. s (bed(w)side\$(w)(cot or cots or cradle\$ or crib or crib)
27. s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 or s26
28. s nicu or nicus or scbu or scbus
29. s (special or intensive or icu\$(w)(newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1)nat\$ or premie or premies)
30. s (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1)nat\$ or premie or premies)(w)unit\$
31. s s28 or s29 or s30
32. s 27 and s31
33. s promotion\$ or promoting or promot\$ or early(w)discharge\$ or patient\$(w)educat\$
34. s (staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$(w2) training
35. s (family or families or parent\$ or mother\$ or father\$ or partner\$(w2)support\$
36. s antenatal(w)educat\$ or ante(w)natal(w)educat\$ or neonatal(w)educat\$ or neo(w)natal(w)educat\$ or prenatal(w)educat\$ or pre(w)natal(w)educat\$ or preconception\$(w)educat\$ or pre(w)conception\$(w)educat\$
37. s postpartum(w)educat\$ or post(w)partum(w)educat\$ or postnatal(w)educat\$ or post(w)natal(w)educat\$
38. s (family or families or parent\$ or mother\$ or father\$ or partner\$(w2)involv\$
39. s (family or families or parent\$ or mother\$ or father\$ or partner\$(w2)attitude\$
40. s (staff or professional\$ or nurse\$ or doctor\$ or physician\$ or midwife\$ or midwife\$(w2) attitude\$
41. s (peer\$ or social\$ or interpersonal\$ or inter(w)personal\$ or midwife\$ or midwife\$ or profession\$ or practitioner\$ or nursing or lactation)(w2)(encourag\$ or motivat\$ or support\$ or guid\$ or counsel\$ or consult\$ or advic\$ or advis\$)
42. s lactation(w2)(consultant\$ or expert\$ or adviser\$ or specialist\$ or advisor\$)
43. s humane(w2)(prematu\$ or pre(w)matu\$ or premie or premies or perinat\$ or peri(w)nat\$ or neonat\$ or neo(w)nat\$(w)care
44. s (tallin or Levin)(w)(method\$ or approach\$ or program\$ or propos\$ or unit\$)
45. s (mother\$ or parent\$ or maternal\$ or famil\$(w)(led or focus\$ or lead\$ or direct\$ or center\$ or centre\$(w)care
46. s abm or ill or bfi or bfhi or nct
47. s association(w2)breastfeeding(w1)mothers or association(w2)breast(w1)feeding(w1)mothers
48. s la(w1)leche(w1)league or national(w1)childbirth(w1)trust
49. s baby(w1)friendly or breaststart or breast(w1)start or beststart or best(w1)start or nidcap
50. s support\$(w)strateg\$ or support\$(w)system\$ or support\$(w)program\$
51. s Neonat\$(w1)Individualised(w1)Developmental(w1)Care(w2)Assessment(w1)Program\$
52. s Neonat\$(w1)Individualized(w1)Developmental(w1)Care(w2)Assessment(w1)Program\$
53. s Newborn\$(w1)Individualised(w1)Developmental(w1)Care(w2)Assessment(w1)Program\$
54. s Newborn\$(w1)Individualized(w1)Developmental(w1)Care(w2)Assessment(w1)Program\$
55. s s33 or s34 or s35 or s36 or s37 or s38 or s39 or s40 or s41 or s42 or s43 or s44 or s45 or s46 or s47 or s48 or s49 or s50 or s51 or s52 or s53 or s54
56. s s31 and s55
57. s s32 or s56

### HEED (Health Economic Evaluations Database) (internet)

The HEED searches were from inception up to 8 August 2007 and identified 214 references.

#### Search 1

1. TI=breastfe\* or breastmilk\* or lactat\* or breast\* fed\* or breast\* feed\*
2. AB=breastfe\* or breastmilk\* or lactat\* or breast\* fed\* or breast\* feed\*
3. KW=breastfe\* or breastmilk\* or lactat\* or breast\* fed\* or breast\* feed\*
4. TI=transitional care AND (maternal\* or mother\* or baby or babies or infant\* or newborn\* or neonat\* or neo nat\* or perinat\* or peri nat\* or premie or premies)
5. AB=transitional care AND (maternal\* or mother\* or baby or babies or infant\* or newborn\* or neonat\* or neo nat\* or perinat\* or peri nat\* or premie or premies)

6. KW=transitional care AND (maternal\* or mother\* or baby or babies or infant\* or newborn\* or neonat\* or neo nat\* or perinat\* or peri nat\* or premie or premies)
7. TI=(breast\* or mother\* or human or maternal\*) AND milk
8. AB=(breast\* or mother\* or human or maternal\*) AND milk
9. KW=(breast\* or mother\* or human or maternal\*) AND milk
10. cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

**4 hits**

### Search 2

1. TI=nursing AND (maternal\* or mother\* or baby or babies or infant\* or newborn\* or neonat\* or neo nat\* or perinat\* or peri-nat\* or premie or premies)
2. AB=nursing AND (maternal\* or mother\* or baby or babies or infant\* or newborn\* or neonat\* or neo nat\* or perinat\* or peri-nat\* or premie or premies)
3. KW=nursing AND (maternal\* or mother\* or baby or babies or infant\* or newborn\* or neonat\* or neo nat\* or perinat\* or peri-nat\* or premie or premies)
4. TI=(maintain\* or maintenance\* or establish\* or begin\* or start\* or commenc\* continu\* or sustain\* or prolong\* or extend\*) AND (milk or breast\* fed\* or breast feed\* or lactat\* or nursing or suck\* or breastfed\* or breastfeed\*)
5. AB=(maintain\* or maintenance\* or establish\* or begin\* or start\* or commenc\* continu\* or sustain\* or prolong\* or extend\*) AND (milk or breast\* fed\* or breast feed\* or lactat\* or nursing or suck\* or breastfed\* or breastfeed\*)
6. KW=(maintain\* or maintenance\* or establish\* or begin\* or start\* or commenc\* continu\* or sustain\* or prolong\* or extend\*) AND (milk or breast\* fed\* or breast feed\* or lactat\* or nursing or suck\* or breastfed\* or breastfeed\*)
7. TI=(milk or breastmilk) AND (donor\* or donat\* or bank\*)
8. AB=(milk or breastmilk) AND (donor\* or donat\* or bank\*)
9. KW=(milk or breastmilk) AND (donor\* or donat\* or bank\*)
10. cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

**2 hits**

### Search 3

1. TI=(milk or breast\*) AND express\*
2. AB=(milk or breast\*) AND express\*
3. KW=(milk or breast\*) AND express\*
4. TI=breast pump\* or breastpump\* or (hand\* AND express\*) or

5. kangaroo or (skin\* AND contact) or (suck\* AND breast\*)
6. AB=breast pump\* or breastpump\* or (hand\* AND express\*) or
7. kangaroo or (skin\* AND contact) or (suck\* AND breast\*)
8. KW=breast pump\* or breastpump\* or (hand\* AND express\*) or
9. kangaroo or (skin\* AND contact) or (suck\* AND breast\*)
10. TI=transition AND breast\*
11. AB=transition AND breast\*
12. KW=transition AND breast\*
13. cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

**3 hits**

### Search 4

1. TI=tube or cup or bottle) OR (feed or fee\*)
2. AB=tube or cup or bottle) OR (feed or fee\*)
3. KW=tube or cup or bottle) OR (feed or fee\*)
4. TI=lactagogue\* or lactogogue\* or Galactagogue\* or caffeine or hops or fenugreek or 'fennel seed\*' or 'blessed thistle' or domperidone or alfalfa
5. AB=lactagogue\* or lactogogue\* or Galactagogue\* or caffeine or hops or fenugreek or 'fennel seed\*' or 'blessed thistle' or domperidone or alfalfa
6. KW=lactagogue\* or lactogogue\* or Galactagogue\* or caffeine or hops or fenugreek or 'fennel seed\*' or 'blessed thistle' or domperidone or alfalfa
7. TI=Sulpiride or metoclopramide or domeperidone or chlorpromazine or oxytocin or 'dopamine antagonist\*' or 'thyrotropine releasing hormone\*' or TRH or 'human growth hormone\*' or creatocrit\*
8. AB=Sulpiride or metoclopramide or domeperidone or chlorpromazine or oxytocin or 'dopamine antagonist\*' or 'thyrotropine releasing hormone\*' or TRH or 'human growth hormone\*' or creatocrit\*
9. KW=Sulpiride or metoclopramide or domeperidone or chlorpromazine or oxytocin or 'dopamine antagonist\*' or 'thyrotropine releasing hormone\*' or TRH or 'human growth hormone\*' or creatocrit\*
10. cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

**0 hits**

### Search 5

1. TI=(nipple\* shield\*) or (breast\* shield\*) or (dropper\* fed\*) or (dropper\* fee\*)
2. AB=(nipple\* shield\*) or (breast\* shield\*) or (dropper\* fed\*) or (dropper\* fee\*)

3. KW=(nipple\* shield\*) or (breast\* shield\*) or (dropper\* fed\*) or (dropper\* fee\*)
4. TI=(spoon fee\*) or (spoon fed\*) or (syringe\* fed\*) or (syringe\* fee\*)
5. AB=(spoon fee\*) or (spoon fed\*) or (syringe\* fed\*) or (syringe\* fee\*)
6. KW=(spoon fee\*) or (spoon fed\*) or (syringe\* fed\*) or (syringe\* fee\*)
7. TI=supplementer\* or pacifier\* or dummy or dummies or soother\* or (non-nutritive suck\*) or (nonnutritive suck\*)
8. AB=supplementer\* or pacifier\* or dummy or dummies or soother\* or (non-nutritive suck\*) or (nonnutritive suck\*)
9. KW=supplementer\* or pacifier\* or dummy or dummies or soother\* or (non-nutritive suck\*) or (nonnutritive suck\*)
10. cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

**0 hits****Search 6**

1. TI=rooming-in or room-in or co-sleep\* or bedshar\* or bed-shar\*
2. AB=(rooming-in or room-in or co-sleep\* or bedshar\* or bed-shar\*)
3. KW=(rooming-in or room-in or co-sleep\* or bedshar\* or bed-shar\*)
4. TI=bedside\* AND (cot or cots or cradle\* or crib or crib)
5. AB=bedside\* AND (cot or cots or cradle\* or crib or crib)
6. KW=bedside\* AND (cot or cots or cradle\* or crib or crib)
7. TI=(bed-side\*) AND (cot or cots or cradle\* or crib or crib)
8. AB=(bed-side\*) AND (cot or cots or cradle\* or crib or crib)
9. KW=(bed-side\*) AND (cot or cots or cradle\* or crib or crib)
10. cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

**0 hits****Search 7**

1. TI=nicu or nicus or scbu or scbus
2. AB=nicu or nicus or scbu or scbus
3. KW=nicu or nicus or scbu or scbus
4. TI=(special or intensive or icu\*) AND (newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo-nat\* or perinat\* or peri-nat\* or premie or premies)
5. cs=1 or 2 or 3 or 4

**86 hits****Search 8**

1. KW=(special or intensive or icu\*) AND (newborn\* or neonat\* or baby or babies or

infant\* or neonat\* or neo-nat\* or perinat\* or peri-nat\* or premie or premies)

**111 hits****Search 9**

1. AB=(special or intensive or icu\*) AND (newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo-nat\* or perinat\* or peri-nat\* or premie or premies)
2. TI=(newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo-nat\* or perinat\* or peri-nat\* or premie or premies) AND unit\*
3. AB=(newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo-nat\* or perinat\* or peri-nat\* or premie or premies) AND unit\*
4. KW=(newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo-nat\* or perinat\* or peri-nat\* or premie or premies) AND unit\*
5. cs=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

**104 hits****PEDE (Paediatric Economic Database Evaluation) (internet)**

The PEDE search covered the date range 1980 to 31/12/2003 and retrieved 42 references. The database was searched on 9 August 2007.

<http://pede.bioinfo.sickkids.on.ca/pede/search.jsp>

1. Breast
2. Lactat
3. transitional care
4. milk
5. hand express
6. kangaroo
7. skin contact
8. skin-to-skin
9. bottle
10. tube
11. cup
12. dropper
13. spoon
14. syringe
15. lactagogue
16. lactagogue
17. Galactagogue
18. Caffeine
19. Hops
20. Fenugreek
21. fennel seed
22. blessed thistle
23. domperidone
24. alfalfa
25. Sulpiride
26. Metoclopramide
27. Domperidone
28. Chlorpromazine
29. Oxytocin

30. dopamine antagonist
31. thyrotropine releasing hormone
32. TRH
33. human growth hormone
34. creatinocrit
35. nipple
36. supplementer
37. pacifier
38. dummy
39. dummies
40. soother
41. non-nutritive
42. suck
43. nonnutritive
44. rooming-in
45. room-in
46. co-sleep
47. bedshar
48. bed-shar
49. bedside
50. bed-side

### Supplementary searches to populate the decision model

#### **Long-term outcomes of necrotising enterocolitis (NEC) or spsis**

#### **NHS Economic Evaluation Database (NHS EED) (up to 2008/02/28 (internal CRD interface))**

The NHS EED search was from 2003 to 28/2/08 and identified 27 references.

51. s nec or (necroti\$(w2)enterocol\$)
52. s longterm(w2)outcome\$ or cerebral\$(w1) pals\$ or cp or little\$(w1)disease\$ or spastic(w1) diplegia\$
53. s (visual\$ or vision or hearing)(w2)(loss or disability\$ or impair\$ or difficult\$ or disorder\$ or defect\$ or deficit\$ or deficienc\$)
54. s Deaf\$ or blind\$ or hypoacusis or hypoacuses or macropsia\$ or metamorphopsia\$ or micropsia or dyslexi\$ or dyspraxi\$ or apraxi\$ or disable\$ or disability\$
55. s Hemeralopia\$ or Amblyopia\$ or Amaurosis(w1)Fugax or Diplopia or Hemianopsia or Photophobia or Scotoma or Low(w1)Vision or mental\$(w1)retard\$
56. s (cognitive\$ or development\$ or intellectual\$ or learning\$(w2)(loss or impair\$ or disability\$ or difficult\$ or disorder\$ or defect\$ or delay\$ or deficit\$ or deficienc\$)
57. s (psychomotor\$ or physical\$ or mobility\$ or psycho(w1)motor\$ or neurodevelopment\$ or neuro(w1)development\$(w2)(loss or impair\$

- or disability\$ or difficult\$ or disorder\$ or defect\$ or delay\$ or deficit\$ or deficienc\$)
58. s s2 or s3 or s4 or s5 or s6 or s7
59. s s1 and s8
60. S premie or premies or pre(w1)term\$ or preterm\$ or prematur\$ or nicu or nicus or scbu or scbus
61. s (special or intensive or icu\$(w)(newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1) nat\$ or premie or premies)
62. s (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1)nat\$ or premie or premies)(w)(unit\$ or ward\$)
63. s s10 or s11 or s12
64. s Meningit\$ or meningococc\$ or arachnoiditis or Meningoencephalitis or pachymeningit\$ leptomeningit\$
65. s (dura(w1)mater or mening\$ or arachnoid(w1) membrane)(w2)(inflam\$ or infect\$)
66. s Bacteremia or Fungemia or septic(w1)shock or sepsis or septic\$ or septicaemia
67. s Blood\$(w1)(poison\$ or infect\$)
68. s (skin\$ or pulmonary or Lung\$ or soft(w1) tissue\$(w1)(infect\$ or inflamm\$)
69. s Bronchopneumonia\$ or Pleuropneumonia\$ or pneumonia\$ or pneumonit\$ or Streptococcal(w1)Infect\$ or Staphylococc\$(w1) Infect\$ or Dermatomycos\$ or Community(w1) Acquired(w1)Infection\$ or Hospital\$(w1) Acquired(w1)Infection\$
70. s (Swan(w1)Ganz or indwelling or in(w1) dwelling or intrarterial or intra(w1)arterial or picc or hickman or subclavian or central or venous or arterial or peripheral or jugular)(w2) (line or lines or catheter\$ port\$)
71. s vascular(w1)access
72. s (joint or spine or spinal or bone\$(w1)(infect\$ or inflamm\$)
73. s Osteitis or osteomyelit\$ or Discit\$ or Periostit\$ or Spondylit\$
74. s (Osteoarticular or Osteo(w1)articular or bone\$ or joint\$ or spine or spinal)(w1) tuberculosis
75. s s14 or s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24
76. s s13 and s25 and s8
77. s s9 or s26

#### **Health Economic Evaluations Database (HEED) (up to 28/02/2008) (internet)**

The HEED search was from 2003 to 28/2/08 and identified 110 references.

**Search 1**

1. nec or necrotizing enterocolitis or necrotising enterocolitis

**13 hits****Expert search****Search 2**

1. AX= pre term or preterm\* or prematur\* or nicu or nicus or scbu or scbus or newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo natal or neo nate or neo nates or neo nately or perinat\* or peri nate or peri nates or peri natal or peri nately or premie or premies
2. AX= Meningit\* or meningococc\* or arachnoiditis or Meningoencephalitis or pachymeningit\* or leptomeningit\* or vascular access or inflam\* or infect\* or Bacteremia or Fungemia or septic shock or sepsis or septic\* or septicaemia or osteomyelit\* or tuberculosis or tubercular or Bronchopneumonia\* or Pleuropneumonia\* or pneumonia\* or pneumonit\* or Streptococcal Infection or Streptococcal or Staphylococcal or Staphylococcus or Dermatomycos\* or Discit\* or Periostit\* or Spondylit\*
3. AX=(Swan Ganz or indwelling or in-dwelling or intrarterial or picc or hickman or subclavian or central or venous or arterial or peripheral or jugular) within 2 (line or lines or catheter\* or port\*)
4. cs=2 or 3
5. cs=1 and 4

**MEDLINE and MEDLINE In-Process Citations (2003–2008/02/wk 2) (OVID)**

The MEDLINE search was from 2003 to wk 2/02/2008 and identified 132 references.

1. exp Enterocolitis, Necrotizing/
2. (nec or necroti\$ enterocol\$).ti,ab.
3. 1 or 2
4. Cerebral Palsy/
5. (longterm outcome\$ or cerebral\$ pals\$ or cp or little\$ disease\$ or spastic diplegia\$).ti,ab.
6. exp Hearing Disorders/
7. exp Vision Disorders/
8. ((visual\$ or vision or hearing) adj3 (loss or disabilit\$ or impair\$ or difficult\$ or disorder\$ or defect\$ or deficit\$ or deficienc\$)).ti,ab.
9. exp Dyslexia/
10. exp Psychomotor Disorders/
11. (long term outcome\$ or Deaf\$ or blind\$ or hypoacusis or hypoacusis or macropsia\$ or metamorphopsia\$ or micropsia or dyslexi\$ or

dyspraxi\$ or apraxi\$ or disabl\$ or disabilit\$).ti,ab.

12. (Hemeralopia\$ or Amblyopia\$ or Amaurosis Fugax or Diplopia or Hemianopsia or Photophobia or Scotoma or Low Vision or mental\$ retard\$).ti,ab.
13. exp Mental Retardation/
14. exp child development disorders, pervasive/ or developmental disabilities/ or exp learning disorders/ or motor skills disorders/ or stereotypic movement disorder/
15. ((cognitive\$ or development\$ or intellectual\$ or learning\$) adj2 (loss or impair\$ or disabilit\$ or difficult\$ or disorder\$ or defect\$ or delay\$ or deficit\$ or deficienc\$)).ti,ab.
16. ((psychomotor\$ or physical\$ or mobility\$ or psycho motor\$ or neurodevelopment\$ or neuro development\$) adj2 (loss or impair\$ or disability\$ or difficult\$ or disorder\$ or defect\$ or delay\$ or deficit\$ or deficienc\$)).ti,ab.
17. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 3 and 17
19. (premie or premies or pre term\$ or preterm\$ or prematur\$ or nicu or nicus or scbu or scbus).ti,ab.
20. infant, premature/
21. intensive care units, neonatal/
22. intensive care, neonatal/
23. ((special or intensive or icu\$) adj3 (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies)).mp.
24. ((newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies) adj2 unit\$).mp.
25. 19 or 20 or 21 or 22 or 23 or 24
26. exp Meningitis/
27. exp sepsis/ or soft tissue infections/
28. exp Skin Diseases, Bacterial/
29. exp Staphylococcal Skin Infections/
30. exp Dermatomycoses/
31. Pseudomonas Infections/
32. exp Pneumonia, Bacterial/
33. soft tissue infections/ or exp urinary tract infections/
34. ((urinar\$ or urine or uret\$) adj2 (infect\$ or inflam\$)).ti,ab.
35. exp Bone Diseases, Infectious/
36. (Osteitior osteomyelit\$ or Discit\$ or Periostit\$ or Spondylit\$).ti,ab.
37. ((Osteoarticular or Osteo articular or bone\$ or joint\$ or spine or spinal) adj1 tuberculosis).ti,ab.
38. or/26-37

39. 25 and 38 and 17
40. 18 or 39
41. ('2003' or '2004' or '2005' or '2006' or '2007' or '2008').yr.
42. 40 and 41

#### EMBASE (2003–2008/wk 7) (OVID)

The EMBASE search was from 2003 to wk 7/2008 and identified 444 references.

1. Necrotizing Enterocolitis/
2. (nec or necroti\$ enterocol\$).ti,ab.
3. 1 or 2
4. (longterm outcome\$ or cerebral\$ pals\$ or cp or little\$ disease\$ or spastic diplegia\$).ti,ab.
5. Cerebral Palsy/
6. exp Hearing Disorder/
7. exp Visual Disorder/
8. ((visual\$ or vision or hearing) adj3 (loss or disabilit\$ or impair\$ or difficult\$ or disorder\$ or defect\$ or deficit\$ or deficienc\$)).ti,ab.
9. dyslexia/ or aphasia/
10. exp Psychomotor Disorder/
11. (long term outcome\$ or Deaf\$ or blind\$ or hypoacusis or hypoacuses or macropsia\$ or metamorphopsia\$ or micropsia or dyslexi\$ or dyspraxi\$ or apraxi\$ or disabl\$ or disabilit\$).ti,ab.
12. (Hemeralopia\$ or Amblyopia\$ or Amaurosis Fugax or Diplopia or Hemianopsia or Photophobia or Scotoma or Low Vision or mental\$ retard\$).ti,ab.
13. exp Mental Deficiency/
14. Developmental Disorder/
15. exp Learning Disorder/
16. exp Motor Dysfunction/
17. ((cognitive\$ or development\$ or intellectual\$ or learning\$) adj2 (loss or impair\$ or disabilit\$ or difficult\$ or disorder\$ or defect\$ or delay\$ or deficit\$ or deficienc\$)).ti,ab.
18. ((psychomotor\$ or physical\$ or mobility\$ or psycho motor\$ or neurodevelopment\$ or neuro development\$) adj2 (loss or impair\$ or disability\$ or difficult\$ or disorder\$ or defect\$ or delay\$ or deficit\$ or deficienc\$)).ti,ab.
19. or/4-18
20. (premie or premies or pre term\$ or preterm\$ or prematur\$ or nicu or nicus or scbu or scbus).ti,ab.
21. ((special or intensive or icu\$) adj3 (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies)).mp.
22. ((newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo nat\$ or perinat\$ or peri nat\$ or premie or premies) adj2 unit\$).mp.
23. newborn intensive care/
24. newborn intensive care nursing/
25. or/20-24
26. exp Meningitis/
27. newborn sepsis/ or sepsis/ or septicemia/ or septic shock/
28. Soft Tissue Infection/
29. exp 'bone and joint infections'/ or exp device infection/ or exp skin infection/
30. exp lung infection/ or exp pneumonia/
31. exp Urinary Tract Infection/
32. ((urinar\$ or urine or uret\$) adj2 (infect\$ or inflam\$)).ti,ab.
33. (Osteitior osteomyelit\$ or Discit\$ or Periostit\$ or Spondylit\$).ti,ab.
34. ((Osteoarticular or Osteo articular or bone\$ or joint\$ or spine or spinal) adj1 tuberculosis).ti,ab.
35. or/26-34
36. 3 and 19
37. 25 and 35 and 19
38. 36 or 37
39. ('2003' or '2004' or '2005' or '2006' or '2007' or '2008').yr.
40. 38 and 39

#### EconLit (2003–2008/01) (OVID)

The EconLit search was from 2003 to 01/2008 and identified zero references.

1. #13 #5 and #12 0
2. #12 #6 and #11 and #4 0
3. #11 #7 or #7 or #8 or #9 or #10 330
4. #10 (Osteoarticular or Osteo articular or bone\* or joint\* or spine or spinal) adj tuberculosis 0
5. #9 ( (Swan Ganz or indwelling or in-dwelling or intrarterial or intra arterial or picc or hickman or subclavian or central or venouor arterial or peripheral or jugular) near (line or lines or catheter\* or port\*) )or( (joint or spine or spinal or bone\* or urin\* or urin\* or uret\*) near (infect\* or inflamm\*) )or( Osteitior osteomyelit\* or Discit\* or Periostit\* or Spondylit\* ) 287
6. #8 ( Blood\* adj (poison\* or infect\*) )or( (skin\* or pulmonary or Lung\* or soft tissue\*) adj (infect\* or inflamm\*) )or( Bronchopneumonia\* or Pleuropneumonia\* or pneumonia\* or pneumonit\* or Streptococcal Infect\* or Staphylococc\* Infect\* or Dermatomycos\* or Community Acquired Infection\* or Hospital\* Acquired Infection\* ) 33

7. #7 ( Meningit\* or meningococc\* or arachnoiditis or Meningoencephalitis or pachymeningit\* or leptomeningit\* or vascular access )or( (dura mater or mening\* or arachnoid membrane)near (inflam\* or infect\*) )or( Bacteremia or Fungemia or septic shock or sepsis or septic\* or septicaemia ) 10
8. #6 ( premie or premies or pre term\* or preterm\* or prematur\* or nicu or nicus or scbu or scbus )or( (special or intensive or icu\*) near (newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo nat\* or perinat\* or peri nat\* or premie or premies) )or( (newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo nat\* or perinat\* or peri nat\* or premie or premies)near (unit\* or ward\*) ) 567
9. #5 #1 and #4 0
10. #4 #2 or #3 4620
11. #3 ( Hemeralopia\* or Amblyopia\* or Amaurosis Fugax or Diplopia or Hemianopsia or Photophobia or Scotoma or Low Vision or mental\* retard\* )or( (cognitive\* or development\* or intellectual\* or learning\*) near (loss or impair\* or disabilit\* or difficult\* or disorder\* or defect\* or delay\* or deficit\* or deficient\*) )or( (psychomotor\* or physical\* or mobility\* or psycho motor\* or neurodevelopment\* or neuro development\*) near (loss or impair\* or disability\* or difficult\* or disorder\* or defect\* or delay\* or deficit\* or deficient\*) ) 1259
12. #2 ( longterm outcome\* or cerebral\* pals\* or cp or little\* disease\* or spastic diplegia\* ) or( (visual\* or vision or hearing) near (loss or disabilit\* or impair\* or difficult\* or disorder\* or defect\* or deficit\* or deficient\*) )or( Deaf\* or blind\* or hypoacusis or hypoacuses or macropsia\* or metamorphopsia\* or micropsia or dyslexi\* or dyspraxi\* or apraxi\* or disable\* or disabilit\* ) 3450
13. #1 nec or necroti\* enterocol\* 25

**Quality of life in babies with NEC, sepsis, meningitis, etc.**

**NHS Economic Evaluation Database (NHS EED) (up to 2008/02/28 (internal CRD interface))**

The NHS EED search was from inception to 28/2/08 and identified 39 references.

1. s nec or (necroti\$(w2)enterocol\$)
2. s Meningit\$ or meningococc\$ or arachnoiditis or Meningoencephalitis or pachymeningit\$ or leptomeningit\$
3. s (dura(w1)mater or mening\$ or arachnoid(w1) membrane)(w2)(inflam\$ or infect\$)

4. s Bacteremia or Fungemia or septic(w1)shock or sepsis or septic\$ or septicaemia
5. s Blood\$(w1)(poison\$ or infect\$)
6. s (skin\$ or pulmonary or Lung\$ or soft(w1) tissue\$(w1)(infect\$ or inflamm\$)
7. s Bronchopneumonia\$ or Pleuropneumonia\$ or pneumonia\$ or pneumonit\$ or Streptococcal(w1)Infect\$ or Staphylococc\$(w1) Infect\$ or Dermatomycos\$ or Community(w1) Acquired(w1)Infection\$ or Hospital\$(w1) Acquired(w1)Infection\$
8. s (Swan(w1)Ganz or indwelling or in(w1) dwelling or intrarterial or intra(w1)arterial or picc or hickman or subclavian or central or venous or arterial or peripheral or jugular)(w2) (line or lines or catheter\$ or port\$)
9. s vascular(w1)access
10. s (joint or spine or spinal or bone\$(w1)(infect\$ or inflamm\$)
11. s Osteitis or osteomyelit\$ or Discit\$ or Periostit\$ or Spondylit\$
12. s (Osteoarticular or Osteo(w1)articular or bone\$ or joint\$ or spine or spinal)(w1) tuberculosis
13. s s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12
14. s quality(w2)life or qol or qaly\$ or hrqol or eq5d or sf6d or sf36d or hui1 or hui or huis or hui2 or hui3 or health(w)utility\$(w1)ind\$
15. s baby or babies or infant\$ or newborn\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1) nat\$ or premie or premies
16. s s13 and s14 and s15

**Health Economic Evaluations Database (HEED) (up to 28/02/2008) (internet)**

The HEED search was from inception to 28/2/08 and identified 60 references.

1. AX= pre term or preterm\* or prematur\* or nicu or nicus or scbu or scbus or newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo natal or neo nate or neo nates or neo nately or perinat\* or peri nate or peri nates or peri natal or peri nately or premie or premies
2. AX= Meningit\* or meningococc\* or arachnoiditis or Meningoencephalitis or pachymeningit\* or leptomeningit\* or vascular access or inflam\* or infect\* or Bacteremia or Fungemia or septic shock or sepsis or septic\* or septicaemia or osteomyelit\* or tuberculosis or tubercular or Bronchopneumonia\* or Pleuropneumonia\* or pneumonia\* or pneumonit\* or Streptococcal Infection or Streptococcal or Staphylococcal or

- Staphylococcus or Dermatomyces\* or Discit\* or Periostit\* or Spondylit\*
- AX='quality of life' or qol or qaly\* or hrqol or eq5d or sf6d or sf36d or hui1 or hui or huis or hui2 or hui3 or 'health utility' or 'health utilities'
  - cs=1 and 2 and 3

### EconLit (2003–01/2008) (OVID)

The EconLit search was from inception to 1/2008 and identified zero references.

- #8 #5 and #6 and #7 0
- #7 Baby or babies or infant\* or newborn\* or neonat\* or neo-nat\* or perinat\* or peri-nat\* or premie or premies 1684
- #6 'quality of life' or qol or qaly\* or hrqol or eq5d or sf6d or sf36d or hui1 or hui or huis or hui2 or hui3 or (health utility\* ind\*) 823

Searches and results below from saved search history scbu\_lto\_econ1b

- #5 #1 or #1 or #2 or #3 or #4 332
- #4 (Osteoarticular or Osteo articular or bone\* or joint\* or spine or spinal) adj tuberculosis 0
- #3 ( Swan Ganz or indwelling or in-dwelling or intrarterial or intra arterial or picc or hickman or subclavian or central or venouor arterial or peripheral or jugular) near (line or lines or catheter\* or port\*) or( (joint or spine or spinal or bone\*) near (infect\* or inflamm\*) )or( Osteitior osteomyelit\* or Discit\* or Periostit\* or Spondylit\* ) 288
- #2 ( Blood\* adj (poison\* or infect\*) )or( (skin\* or pulmonary or Lung\* or soft tissue\*) adj (infect\* or inflamm\*) )or( Bronchopneumonia\* or Pleuropneumonia\* or pneumonia\* or pneumonit\* or Streptococcal Infect\* or Staphylococ\* Infect\* or Dermatomyces\* or Community Acquired Infection\* or Hospital\* Acquired Infection\* ) 34
- #1 ( Meningit\* or meningococc\* or arachnoiditis or Meningoencephalitis or pachymeningit\* or leptomeningit\* or vascular access )or( (dura mater or mening\* or arachnoid membrane)near (inflam\* or infect\*) )or( Bacteremia or Fungemia or septic shock or sepsis or septic\* or septicaemia ) 10

### **Economic evaluations of NEC, sepsis, meningitis, etc. in preterms or SCBUs NHS Economic Evaluation Database (NHS EED) (up to 28/02/2008; internal CRD interface)**

The NHS EED search was from inception to 28/2/08 and identified 43 references.

- s (premie or premies or pre(w1)term\$ or preterm\$ or prematur\$)
- s nicu or nicus or scbu or scbus
- s (special or intensive or icu\$(w)(newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1)nat\$ or premie or premies)
- s (newborn\$ or neonat\$ or baby or babies or infant\$ or neonat\$ or neo(w1)nat\$ or perinat\$ or peri(w1)nat\$ or premie or premies)(w)(unit\$ or ward\$)
- s s1 or s2 or s3 or s4
- s nec or (necroti\$(w2)enterocol\$)
- s Meningit\$ or meningococc\$ or arachnoiditis or Meningoencephalitis or pachymeningit\$ or leptomeningit\$
- s (dura(w1)mater or mening\$ or arachnoid(w1)membrane)(w2)(inflam\$ or infect\$)
- s Bacteremia or Fungemia or septic(w1)shock or sepsis or septic\$ or septicaemia
- s Blood\$(w1)(poison\$ or infect\$)
- s (skin\$ or pulmonary or Lung\$ or soft(w1)tissue\$(w1)(infect\$ or inflamm\$)
- s Bronchopneumonia\$ or Pleuropneumonia\$ or pneumonia\$ or pneumonit\$ or Streptococcal(w1)Infect\$ or Staphylococ\$(w1)Infect\$ or Dermatomyces\$ or Community(w1)Acquired(w1)Infection\$ or Hospital\$(w1)Acquired(w1)Infection\$
- s (Swan(w1)Ganz or indwelling or in(w1)dwelling or intrarterial or intra(w1)arterial or picc or hickman or subclavian or central or venous or arterial or peripheral or jugular)(w2)(line or lines or catheter\$ or port\$)
- s vascular(w1)access
- s (joint or spine or spinal or bone\$(w1)(infect\$ or inflamm\$)
- s Osteitis or osteomyelit\$ or Discit\$ or Periostit\$ or Spondylit\$
- s (Osteoarticular or Osteo(w1)articular or bone\$ or joint\$ or spine or spinal)(w1)tuberculosis
- s s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17
- s s5 and s18

### **Health Economic Evaluations Database (HEED) (up to 28/12/2008) (internet)**

The HEED search was from inception to 28/2/08 and identified 443 references.

#### **Search 1**

- nec or necrotizing enterocolitis or necrotising enterocolitis

**13 hits**



**Expert search****Search 2**

1. AX= pre term or preterm\* or prematur\* or nicu or nicus or scbu or scbus or newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo natal or neo nate or neo nates or neo nately or perinat\* or peri nate or peri nates or peri natal or peri nately or premie or premies
2. AX= Meningit\* or meningococc\* or arachnoiditis or Meningoencephalitis or pachymeningit\* or leptomeningit\* or vascular access or inflam\* or infect\* or Bacteremia or Fungemia or septic shock or sepsis or septic\* or septicaemia or osteomyelit\* or tuberculosis or tubercular or Bronchopneumonia\* or Pleuropneumonia\* or pneumonia\* or pneumonit\* or Streptococcal Infection or Streptococcal or Staphylococcal or Staphylococcus or Dermatomycos\* or Discit\* or Periostit\* or Spondylit\*
3. AX=(Swan Ganz or indwelling or in-dwelling or intrarterial or picc or hickman or subclavian or central or venous or arterial or peripheral or jugular) within 2 (line or lines or catheter\* or port\*)
4. cs=2 or 3
5. cs=1 and 4

**EconLit (2003–01/2008) (OVID)**

The EconLit search was from inception to 01/2008 and identified one reference.

1. #9 #2 and #8 1
2. #8 #7 or #1 357

Searches and results below from saved search history scbu\_lto\_econ1b

3. #7 #3 or #3 or #4 or #5 or #6 332
4. #6 (Osteoarticular or Osteo articular or bone\* or joint\* or spine or spinal) adj tuberculosis 0
5. #5 ( (Swan Ganz or indwelling or in-dwelling or intrarterial or intra arterial or picc or hickman or subclavian or central or venous or arterial or peripheral or jugular) near (line or lines or catheter\* or port\*) )or( (joint or spine or spinal or bone\*) near (infect\* or inflam\*) )or( Osteitior osteomyelit\* or Discit\* or Periostit\* or Spondylit\* ) 288
6. #4 ( Blood\* adj (poison\* or infect\*) )or( (skin\* or pulmonary or Lung\* or soft tissue\*) adj (infect\* or inflam\*) )or( Bronchopneumonia\* or Pleuropneumonia\* or pneumonia\* or pneumonit\* or Streptococcal Infect\* or Staphylococc\* Infect\* or Dermatomycos\* or

Community Acquired Infection\* or Hospital\* Acquired Infection\* ) 34

7. #3 ( Meningit\* or meningococc\* or arachnoiditis or Meningoencephalitis or pachymeningit\* or leptomeningit\* or vascular access )or( (dura mater or mening\* or arachnoid membrane)near (inflam\* or infect\*) )or( Bacteremia or Fungemia or septic shock or sepsis or septic\* or septicaemia ) 10
8. #2 ( premie or premies or pre term\* or preterm\* or prematur\* or nicu or nicus or scbu or scbus )or( (special or intensive or icu\*) near (newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo nat\* or perinat\* or peri nat\* or premie or premies) )or( (newborn\* or neonat\* or baby or babies or infant\* or neonat\* or neo nat\* or perinat\* or peri nat\* or premie or premies)near (unit\* or ward\*) ) 568
9. #1 nec or necroti\* enterocol\* 25

## Appendix 2.3: Additional search strategies for economic modelling

### Searches of health economics resources

The following resources were searched to identify economic evaluations for inclusion in the review and to inform the decision modelling:

NHS Economic Evaluation Database (NHS EED) (up to 2007/08/8) (internal CRD interface)  
Health Economic Evaluations Database (HEED) (up to 2007/08/08) (internet)  
Pediatric Economic Database Evaluation (PEDE) (1980–2003) (internet) (<http://pede.bioinfo.sick-kids.on.ca/pede.index.jsp>).

A total of 294 references was retrieved.

### Subset search of Clinical Effectiveness Endnote Library

An Endnote Library containing 10,262 references, identified by the search undertaken for the evidence of effectiveness review search detailed above, was searched to identify potentially relevant cost/economic studies. After deduplication, 1176 records were identified.

The following terms were entered line-by-line ( \_ indicates a space):

- \_cost\_
- \_costs

- \_cost-
- \_costly
- \_costing
- \_econom
- \_budget
- \_price
- \_pricing
- \_expenditure
- value for money.

A total of 1176 references was retrieved and scanned for relevance.

### **Further searches to populate the decision model**

A series of focused supplementary searches were undertaken to identify data to populate the model. These searches were limited to a small collection of 'core' databases, as specified by the Health Economists:

- NHS Economic Evaluation Database (NHS EED) (up to 2008/02/28) (internal CRD interface)

- Health Economic Evaluations Database (HEED) (up to 2008/02/28) (internet)
- MEDLINE and MEDLINE In-Process Citations (2003–2008/02/wk 2) (OVID)
- Embase (2003–2008/wk 7) (OVID)
- EconLit (2003–2008/01) (OVID).

Searches were undertaken for three supplementary topics:

- long-term outcomes of necrotising enterocolitis (NEC) or sepsis
- quality of life in babies with NEC, sepsis, meningitis, etc.
- economic evaluations of NEC, sepsis, meningitis, etc. in preterms or SCBUs.

Totals of 713, 99 and 487 references, respectively, were retrieved for the searches and scanned for relevance.



# Health Technology Assessment reports published to date

**Volume 1, 1997****No. 1**

Home parenteral nutrition: a systematic review.

By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

**No. 2**

Diagnosis, management and screening of early localised prostate cancer.

A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

**No. 3**

The diagnosis, management, treatment and costs of prostate cancer in England and Wales.

A review by Chamberlain J, Melia J, Moss S, Brown J.

**No. 4**

Screening for fragile X syndrome.

A review by Murray J, Cuckle H, Taylor G, Hewison J.

**No. 5**

A review of near patient testing in primary care.

By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al.*

**No. 6**

Systematic review of outpatient services for chronic pain control.

By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

**No. 7**

Neonatal screening for inborn errors of metabolism: cost, yield and outcome.

A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al.*

**No. 8**

Preschool vision screening.

A review by Snowdon SK, Stewart-Brown SL.

**No. 9**

Implications of socio-cultural contexts for the ethics of clinical trials.

A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

**No. 10**

A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.

By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

**No. 11**

Newborn screening for inborn errors of metabolism: a systematic review.

By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al.*

**No. 12**

Routine preoperative testing: a systematic review of the evidence.

By Munro J, Booth A, Nicholl J.

**No. 13**

Systematic review of the effectiveness of laxatives in the elderly.

By Petticrew M, Watt I, Sheldon T.

**No. 14**

When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.

A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

**Volume 2, 1998****No. 1**

Antenatal screening for Down's syndrome.

A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

**No. 2**

Screening for ovarian cancer: a systematic review.

By Bell R, Petticrew M, Luengo S, Sheldon TA.

**No. 3**

Consensus development methods, and their use in clinical guideline development.

A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al.*

**No. 4**

A cost-utility analysis of interferon beta for multiple sclerosis.

By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

**No. 5**

Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.

By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al.*

**No. 6**

Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.

By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

**No. 7**

Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.

By Song F, Glenny AM.

**No. 8**

Bone marrow and peripheral blood stem cell transplantation for malignancy.

A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

**No. 9**

Screening for speech and language delay: a systematic review of the literature.

By Law J, Boyle J, Harris F, Harkness A, Nye C.

**No. 10**

Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.

By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

**No. 11**

Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.

By Ebrahim S.

**No. 12**

Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.

By McQuay HJ, Moore RA.

**No. 13**

Choosing between randomised and nonrandomised studies: a systematic review.

By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

**No. 14**

Evaluating patient-based outcome measures for use in clinical trials.

A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

**No. 15**

Ethical issues in the design and conduct of randomised controlled trials.

A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

**No. 16**

Qualitative research methods in health technology assessment: a review of the literature.

By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

**No. 17**

The costs and benefits of paramedic skills in pre-hospital trauma care.

By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

**No. 18**

Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.

By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al.*

**No. 19**

Systematic reviews of trials and other studies.

By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

**No. 20**

Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.

A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al.*

**Volume 3, 1999**

**No. 1**

Informed decision making: an annotated bibliography and systematic review.

By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al.*

**No. 2**

Handling uncertainty when performing economic evaluation of healthcare interventions.

A review by Briggs AH, Gray AM.

**No. 3**

The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.

By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

**No. 4**

A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.

By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al.*

**No. 5**

Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.

By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

**No. 6**

Assessing the costs of healthcare technologies in clinical trials.

A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

**No. 7**

Cooperatives and their primary care emergency centres: organisation and impact.

By Hallam L, Henthorne K.

**No. 8**

Screening for cystic fibrosis.

A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

**No. 9**

A review of the use of health status measures in economic evaluation.

By Brazier J, Deverill M, Green C, Harper R, Booth A.

**No. 10**

Methods for the analysis of quality-of-life and survival data in health technology assessment.

A review by Billingham LJ, Abrams KR, Jones DR.

**No. 11**

Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.

By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

**No. 12**

Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.

A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al.*

**No. 13**

'Early warning systems' for identifying new healthcare technologies.

By Robert G, Stevens A, Gabbay J.

**No. 14**

A systematic review of the role of human papillomavirus testing within a cervical screening programme.

By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al.*

**No. 15**

Near patient testing in diabetes clinics: appraising the costs and outcomes.

By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

**No. 16**

Positron emission tomography: establishing priorities for health technology assessment.

A review by Robert G, Milne R.

**No. 17 (Pt 1)**

The debridement of chronic wounds: a systematic review.

By Bradley M, Cullum N, Sheldon T.

**No. 17 (Pt 2)**

Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.

By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

**No. 18**

A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.

By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al.*

**No. 19**

What role for statins? A review and economic model.

By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al.*

**No. 20**

Factors that limit the quality, number and progress of randomised controlled trials.

A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al.*

**No. 21**

Antimicrobial prophylaxis in total hip replacement: a systematic review.

By Glenny AM, Song F.

**No. 22**

Health promoting schools and health promotion in schools: two systematic reviews.

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