Abstract

Introduction: Babies born before 30 weeks’ gestation are at increased risk of major clinical complications and have greater nutritional requirements. Where nutritional requirements cannot be sufficiently provided for by the mother’s own milk (MOM), routine care in England uses cow milk-derived fortifiers and formulas. However, the use of cow milk in the diets of preterm babies has been associated with adverse health outcomes. Clinical trials have shown that an exclusive human milk diet (EHMD) – where MOM is supplemented by donor human milk-derived formulas and fortifiers – has the potential to be clinically beneficial and reduce the risk of complications.

Objectives: This study has two key objectives: 1) estimate the cost-effectiveness of an EHMD for babies born before 30 weeks’ gestation, relative to routine care; 2) estimate the budget impact of adopting EHMDs in practice in England.

Methods: The analysis will use a modelling approach based on the most relevant data available. The population will consist of babies born in England before 30 weeks’ gestation. Babies in the intervention arm will be simulated to represent outcomes associated with babies fed an EHMD, and those in the comparator arm to receive routine care. Model parameters will be drawn from three sources: i) a recently completed randomised clinical trial, ii) the National Neonatal Research Database, and iii) published literature. The model will adopt a time horizon of two years following initial admission to a neonatal unit. The primary outcome for the cost-effectiveness analysis will be the incremental cost per life-year gained (if observed) associated with the intervention, relative to the comparator. We will also present disaggregated outcomes in a cost-consequence analysis. The primary outcome for the budget impact analysis will be the total cost associated with EHMD compared with current practice from the
perspective of the English National Health Service (NHS).

**Keywords**
human milk, diet, neonatal, nutrition, cost-effectiveness, budget impact, preterm infants

This article is included in the Agriculture, Food and Nutrition gateway.

**Corresponding author:** Chris Sampson (csampson@ohe.org)

**Author roles:** Sampson C: Conceptualization, Funding Acquisition, Methodology, Project Administration, Writing – Original Draft Preparation, Writing – Review & Editing; Zhang K: Conceptualization, Methodology, Writing – Original Draft Preparation; Parkin D: Methodology, Writing – Review & Editing; Hampson G: Methodology, Writing – Review & Editing

**Competing interests:** The authors assert that they have no known competing interests. The authors acknowledge that the products to be evaluated in this study are manufactured by the funder of the study.

**Grant information:** This study was commissioned and funded by Prolacta Bioscience.

**Copyright:** © 2021 Sampson C et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Sampson C, Zhang K, Parkin D and Hampson G. Exclusive human milk diet for very preterm babies in England: protocol for a cost-effectiveness and budget impact analysis [version 1; peer review: 1 approved, 1 approved with reservations] F1000Research 2021, 10:21 https://doi.org/10.12688/f1000research.22450.1

**First published:** 13 Jan 2021, 10:21 https://doi.org/10.12688/f1000research.22450.1
**Background**

Babies born before 30 weeks’ gestation are at increased risk of major clinical complications including necrotising enterocolitis (NEC), sepsis, and mortality. The clinical management of preterm babies is complicated by their having greater nutritional requirements than full-term babies. In many cases, the mothers’ own milk (MOM) is not sufficient – in volume or nutritional content – to meet preterm babies’ needs. Consequently, both preterm formulas and milk fortifiers are used to feed preterm infants.

In England, routinely used fortifiers and formulas are derived from cow milk. The use of cow milk-derived fortifier (CMDF) in the diet of preterm infants has been shown to be associated with several adverse health outcomes. Clinical trials have demonstrated that an exclusive human milk diet (EHMD), based on a MOM alongside fortifiers and formulas manufactured from donor human milk, may be clinically beneficial. An EHMD has been associated with reduced risk of negative sequelae such as NEC, sepsis, neurodevelopmental problems, and lung disease.

A randomised controlled trial was recently completed in England, sponsored by Newcastle Hospitals NHS Foundation Trust. The *Interactions between the diet and gut microbes and metabolism in preterm infants* (INDIGO) study sought to evaluate EHMDs in the English setting in terms of its impact on gut bacteria and body composition. The INDIGO trial also recorded data relating to health care resource use and clinical endpoints.

An EHMD, where human milk-derived fortifier (HMDF) and formula are provided (where MOM is insufficient for the preterm infant’s nutritional needs), is likely to be associated with higher upfront costs for the provision of nutrition. However, the major cost of neonatal care in England is attributable to time spent in a neonatal unit (NNU). If an EHMD reduced the time spent in the NNU, it could reduce costs overall.

Previous studies have evaluated the cost-effectiveness of an EHMD for low birth weight babies in the United States and found that it is likely to reduce mortality and reduce costs by reducing adverse clinical events. However, there are important differences between the United States and the National Health Service (NHS) context in England, which mean that the findings may not be applicable. No previous studies have estimated the cost-effectiveness of an EHMD for low birth weight babies in England.

**Methods**

The aim of this analysis is to estimate the expected cost-effectiveness of an EHMD for preterm babies in England, and the budget impact of adopting its use in practice. The analysis will use a modelling approach based on the most relevant data available.

**Population, interventions, and outcomes**

The population will be babies born in England before 30 weeks’ gestation, which aligns with the inclusion criteria used in the INDIGO trial. The population will represent a complete cohort of babies admitted to NNUs in England within one year.

Babies in the intervention arm are fed with MOM, supplemented with HMDFs (Humavant®+6 human milk fortifier [human, pasteurized], Prolacta Bioscience) with or without human milk-derived ready-to-feed preterm formula (Humavant® RTF 26 human milk-based premature infant formula, Prolacta Bioscience). The intervention arm is henceforth referred to as EHMD.

Babies in the comparator arm are fed with MOM, supplemented with CMDFs with or without cow milk-derived ready-to-feed formula. This comparator is intended to represent usual care in England, though usual care can vary between hospitals.

The cost-effectiveness analysis will estimate the cost per life-year associated with the intervention and comparator, using the best available evidence. If an EHMD is associated with improved outcomes and greater costs, its cost-effectiveness will be estimated as the cost per life year gained. This analysis will be conducted from the perspective of the NHS in England.

A secondary analysis will consider disaggregated outcomes in the form of a cost-consequence analysis. These outcomes will include counts of key events including death and several diagnostic indicators as described below.

As with the cost-effectiveness analysis, the budget impact of an EHMD will be estimated from the perspective of the NHS in England. This will be summarised as the total incremental cost based on health care costs associated with nutritional provision, and complications that incur service use. Costs will also be presented in a disaggregated form to guide decision-making at different levels (e.g., national and local).

The time horizon for the analysis will be two years from baseline, where baseline is initial admission to an NNU. Costs will be discounted at an annual rate of 3.5% for the cost-effectiveness analysis in accordance with methodological guidance published by the National Institute for Health and Care Excellence (NICE). Discounting will not be applied for the budget impact analysis.

**Data and analysis**

The overall approach for the analysis will be a model-based cost-effectiveness analysis. We will construct an individual sampling model to simulate clinical pathways and disease events for individual babies. The study is informed by published methods and reporting guidance, as set out in principles of good practice in state-transition modelling, budget impact analysis, and reporting for economic evaluations of health interventions. The model will be developed using Microsoft Excel (Microsoft 365 version).

**Model structure**

We will develop a probabilistic discrete-time state-transition microsimulation. The cycle length for the model will be one day. We will conduct 10,000 Monte Carlo simulations for the...
purpose of probabilistic sensitivity analysis. Each simulation will count the occurrence of events and sum costs over the time horizon.

The state-based transition model will have seven states, made up of four levels of neonatal care – intensive, high dependency, special, and transitional – inpatient hospital care, home, and death, as shown in Figure 1. Each state will be associated with a per-cycle cost. Each day in a neonatal care state will also be associated with a cost of nutrition.

Informed by the modelling exercise reported by Seaton et al., we will assume that infants born before 30 weeks’ gestation are transferred to one of three levels of neonatal care: intensive care, high dependency care, or special care, and that subsequent transitions are to lower levels of dependency. While this may not always be the case in practice, the key driver of health care costs is likely to be length of stay, rather than the specific pathway, and so we do not anticipate that this simplifying assumption will introduce substantial bias to our cost estimates.

Transitions are modelled from any neonatal care state to any post-discharge state. An unpopulated transition matrix is shown in Table 1.

A set of events can occur before a baby is discharged from neonatal care. Our model will include the following events:

- Surgical treatment for NEC
- Diagnosis of late-onset sepsis
- Diagnosis of short bowel syndrome
- Diagnosis of bronchopulmonary dysplasia (BPD)
- Diagnosis of retinopathy of prematurity (ROP)
- Diagnosis of neurosensory impairment

The probability of these events occurring will be assumed to be fixed across the different levels of care but to be potentially co-dependent on other events. For instance, the probability of short bowel syndrome and BPD will be associated with the occurrence and treatment of NEC. Stochastic occurrence of all

Figure 1. Model structure.

Table 1. Transition matrix. Black cells represent transitions with zero probability. White cells represent transitions with positive probability. Grey cells represent the probability of no transition.
possible events will be recorded within each cycle of each simulation. Each event will be associated with a cost, if relevant.

**Parameters**

Table 2 shows the list of parameters that will be required by the model and their candidate sources. Transition probabilities, event probabilities, and diet-specific costs will depend on treatment allocation.

As part of the INDIGO trial, data were collected for participants, both directly and through the National Neonatal Research Database (NNRD). The variables available from the INDIGO trial are shown in Table 3.

Collection and analysis of variables as part of the INDIGO study was approved by the North East – Tyne & Wear South Research Ethics Committee (REC reference 17/NE/0169).

The key driver of total costs is likely to be the length of stay in the NNU. The INDIGO data will be used to estimate daily transition probabilities between different levels of care, assuming that babies are admitted to the highest level of care observed.

| Parameter | Anticipated source(s) |
|-----------|-----------------------|
| Baseline characteristics | |
| Population size | NNRD |
| Birth weight | NNRD |
| Gestation length (in weeks) | NNRD |
| Initial state | NNRD |
| Transition probabilities (dependent on allocation) | |
| From intensive care | |
| To high dependency care | INDIGO |
| To special care | INDIGO |
| To transitional care | INDIGO |
| To inpatient care | INDIGO |
| To home | INDIGO |
| To dead | INDIGO, NNRD, literature¹⁵ |
| From high dependency care | |
| To special care | INDIGO |
| To transitional care | INDIGO |
| To inpatient care | INDIGO |
| To home | INDIGO |
| To dead | INDIGO, NNRD, literature¹⁵ |
| From special care | |
| To transitional care | INDIGO |
| To inpatient care | INDIGO |
| To home | INDIGO |
| To dead | INDIGO, NNRD, literature¹⁵ |
| Parameter | Anticipated source(s) |
|-----------|-----------------------|
| From transitional care |  |
| To inpatient care | INDIGO |
| To home | INDIGO |
| To dead | INDIGO, NNRD, literature |
| From inpatient care |  |
| To home | INDIGO, NNRD, literature |
| To dead | INDIGO, NNRD, literature |
| From home |  |
| To inpatient care | Literature |
| To dead | Literature |
| Event probabilities during NNU (dependent on allocation) |  |
| Surgical treatment of NEC | Literature$^1,6$ |
| Diagnosis of late onset sepsis | Literature$^2,6$ |
| Diagnosis of short bowel syndrome (following NEC) | Literature$^7$ |
| Diagnosis of BPD | Literature$^6,18$ |
| Diagnosis of ROP | Literature$^9,20$ |
| Diagnosis of neurosensory impairment | Literature$^{21}$ |
| Resource use (dependent on allocation) |  |
| Humavant+6 quantity per day | INDIGO |
| Humavant RTF 26 quantity per day | INDIGO |
| Formula quantity per day | INDIGO, literature$^2$ |
| Parenteral nutrition | INDIGO, literature |
| Humavant+6 price | Provided by Prolacta Bioscience |
| Humavant RTF 26 price | Provided by Prolacta Bioscience |
| Intensive care day | INDIGO, NHS Reference Costs |
| High dependency care day | INDIGO, NHS Reference Costs |
| Special care day | INDIGO, NHS Reference Costs |
| Transitional care day | INDIGO, NHS Reference Costs |
| Inpatient care day | INDIGO, NHS Reference Costs |
| Surgical interventions | INDIGO, NHS Reference Costs |

Abbreviations: NNRD – National Neonatal Research Database; INDIGO – Interactions between the diet and gut microbes and metabolism in preterm infants (study); NNU – neonatal unit; NHS – National Health Service; NEC – necrotising enterocolitis; BPD – bronchopulmonary dysplasia; ROP – retinopathy of prematurity; RTF – ready-to-feed
The INDIGO data will also be used to estimate the cost of nutrition associated with each comparator, based on the quantity of Humavant+6 fortifier, Humavant RTF 26 premature infant formula, and other formula provided.

Key clinical inputs for this project will be sought through collaboration with clinical experts and from existing publications of previous research. Published sources used will include studies focusing on the prevalence and prognosis of complications associated with very premature babies (for example, (e.g. 21), as well as the outcomes of procedures (e.g. surgery) used to address these complications (e.g. 16). We will source papers that report estimates that most closely correspond to parameters required by our model, will use evidence from England wherever available, and will also prioritise more recent data over older data.

We will use NNRD data to define the population and to support external validation of our model. The extracted data items will be at the individual level, as described in Table 4.

The size of the population will be determined by the NNRD population, which we will assume to be equal to the number of eligible babies born in England for the one-year period from 1 January 2019 to 31 December 2019. Each baby simulated by the model will be attributed a birth weight and gestation length at birth, which will be used to determine the amount of feed required. The comparator group will be simulated to be of the same size and birth characteristics. The NNRD data will also define the proportion of babies allocated to intensive, high dependency, or special care at initial admission to the NNU.

We will compare our estimates with nationally representative data from NNRD to externally validate the estimates of our model with respect to clinical outcomes and resource use.

An application has been submitted to a national Research Ethics Committee for the use of NNRD data for the budget impact analysis. This study will involve analysis of data already collected by the NNRD, with no novel data collection or identifiable information used.

Cost-effectiveness
The time horizon for both the cost-effectiveness analysis and the budget impact analysis will be two years following admission to the NNU. Costs will be calculated from the perspective of the NHS using a combination of data from the INDIGO clinical trial and NHS Reference Costs.

The key outcome of the cost-effectiveness model will be the incremental cost per life-year gained for preterm babies fed with an EHMD, relative to those receiving standard care. Costs considered will include upfront costs associated with providing an EHMD, as well as costs of health care resource use associated with common clinical complications in preterm babies, including BPD and ROP. Only directly incurred costs associated with these clinical events will be included.

Budget impact
The budget impact will be calculated as the difference in total cost between a scenario where babies are fed an EHMD, and one in which CMDFs (with or without cow milk-derived read-to-feed formula) are used. Cost items included will be the same as those for the cost-effectiveness model.

The budget impact analysis will adopt a payer (NHS) perspective. The time horizon will be two years post-admission. The model will evaluate additional costs arising from the switch to a more expensive feeding regime against potential reductions in costs associated with lower health care resource use as a result of improved health outcomes and lower rates of complications (if observed).

The increase in costs associated with an EHMD consist of the additional (total) cost of human milk supplementation, which in turn will depend on the additional cost per day of human milk supplementation, the length of time supplementation is required, and the size of the target population. Cost reductions may arise from improved health outcomes for very preterm babies, with reductions in morbidity, surgical procedures (and associated complications), along with reduced length of stay in enhanced care facilities.
Table 4. National Neonatal Research Database (NNRD) data items.

| Baby demographics (Standard)                  |
|---------------------------------------------|
| Birth weight                                |
| Gestation length (at delivery)              |

| Admission details                           |
|---------------------------------------------|
| Primary category of care required on admission to neonatal critical care |

| Discharge details                           |
|---------------------------------------------|
| Destination on discharge from neonatal critical care (level of care) |
| Transferred for further care type (level of care) |
| Receiving oxygen therapy on discharge indicator (Y/N) |

| Procedures recorded at discharge           |
|---------------------------------------------|
| Procedure (OPCS recorded on discharge from neonatal critical care) |

| Screening                                   |
|---------------------------------------------|
| Laparotomy for necrotising enterocolitis indication code (from abdominal x-rays) |
| Retinopathy of prematurity screening outcome status code |

| Daily care                                  |
|---------------------------------------------|
| Procedure (OPCS on neonatal critical care daily care date) |
| Parenteral nutrition received indicator     |
| Enteral feed type given                     |
| Formula milk or milk fortifier type         |
| Total volume of milk received               |
| Sepsis suspected indicator                  |

| Patient level derived data items            |
|---------------------------------------------|
| Critical care length of stay                |
| Diagnosis of BPD (NNAP definition)          |
| Diagnosis of NEC (NNAP definition)          |
| Diagnosis of neurodevelopmental impairments (NNAP definition) |
| Age at death                                |

Abbreviations: NNAP – National Neonatal Audit Programme; NEC – necrotising enterocolitis; BPD – bronchopulmonary dysplasia

The overall budget impact will be presented as a net cost (or saving) to NHS England.

Sensitivity analyses
As a sensitivity analysis, we will conduct a within-trial analysis using only INDIGO trial data in combination with unit cost estimates.

Validation
Estimates generated by our model will be compared to estimates from NNRD as a means of externally validating our model. We will compare the following between NNRD and our model’s estimates for the usual care arm:
- Mean length of stay in NNU
- Number of surgical NEC cases
- Number of diagnoses of ROP
- Number of sepsis diagnoses

Disseminations of information
Findings of this study will be published in a peer-reviewed journal or other publishing platform.
Study status. The study is in the initial planning stages, with early development of the model. The researchers have not yet accessed any data to be analysed as part of the study. Funding for the study is secured and the study has provisional approval from the Neonatal Data Analysis Unit (subject to ethical approval) to access NNRD data.

Discussion
This study is the first economic evaluation of EHMD use for very preterm babies in England. Given the potential for EHMD to reduce the incidence of health complications associated with significant costs to the health system – as shown in a previous evaluation for the United States – it may represent significantly reduced costs for the NHS and alleviate pressure on neonatal care resources. Beyond cost considerations, this intervention has the potential to bring about significant improvements in quality of life for preterm babies and, by association, their carers.

By using the results of a recent clinical trial for an EHMD in England, as well as costs specific to the English setting, the findings here will be highly relevant to decision-making about whether to use EHMD in the NHS. The inclusion of both a cost-consequence and budget impact analysis will allow us to illustrate a more comprehensive picture of the overall impact of an EHMD on the NHS.

Data availability
Underlying data
No data are associated with article.

Acknowledgments
We are grateful to Prof Nicholas Embleton for the expert opinion provided during the development of our study. Any errors or omissions are our own.

References
1. Patel RM, Kandefer S, Walsh MC, et al.: Causes and Timing of Death in Extremely Premature Infants from 2000 through 2011. N Engl J Med. 2015; 372(4): 331-40. PubMed Abstract | Publisher Full Text | Free Full Text
2. Abrams SA, Schanler RJ, Lee ML, et al.: Greater Mortality and Morbidity in Extremely Preterm Infants Fed a Diet Containing Cow Milk Protein Products. Breastfed Med. 2014; 9(6): 281-5. PubMed Abstract | Publisher Full Text | Free Full Text
3. Sullivan S, Schanler RJ, Kim JH, et al.: An Exclusively Human Milk-Based Diet Is Associated with a Lower Rate of Necrotizing Enterocolitis than a Diet of Human Milk and Bovine Milk-Based Products. J Pediatr. 2010; 156(4): 562-567.e1. PubMed Abstract | Publisher Full Text
4. Cristofalo EA, Schanler RJ, Blanco CL, et al.: Randomized Trial of Exclusive Human Milk versus Preterm Formula Diets in Extremely Premature Infants. J Pediatr. 2013; 163(6): 1592-1595.e1. PubMed Abstract | Publisher Full Text
5. Bucke A, Taylor C: Cost and Cost-Effectiveness of Donor Human Milk to Prevent Necrotizing Enterocolitis: Systematic Review. Breastfed Med. 2017; 12(9): 528-36. PubMed Abstract | Publisher Full Text
6. Hair AB, Peluso AM, Hawthorne KM, et al.: Beyond Necrotizing Enterocolitis Prevention: Improving Outcomes with an Exclusive Human Milk-Based Diet. Breastfed Med. 2016; 11(2): 70-4. PubMed Abstract | Publisher Full Text | Free Full Text
7. Embleton N: Interactions between diet and gut microbes in preterm infants. ISRCTN: 2017 (cited 2020 Apr 16). Publisher Full Text
8. Hampson G, Roberts SLE, Lucas A, et al.: An economic analysis of human milk supplementation for very low birth weight babies in the USA. BMC Pediatr. 2019; 19(1): 337. PubMed Abstract | Publisher Full Text | Free Full Text
9. Ganapathy V, Hay JW, Kim JH: Costs of Necrotizing Enterocolitis and Cost-Effectiveness of Exclusively Human Milk-Based Products in Feeding Extremely Premature Infants. Breastfed Med. 2012; 7(1): 29-37. PubMed Abstract | Publisher Full Text
10. Johnson TJ, Patel AL, Bigger HR, et al.: Economic Benefits and Costs of Human Milk Feedings: A Strategy to Reduce the Risk of Prematurity-Related Morbidities in Very-Low-Birth-Weight Infants. Adv Nutr. 2014; 5(2): 207-12. PubMed Abstract | Publisher Full Text | Free Full Text
11. Sullivan SD, Mauskopf JA, Augustovski F, et al.: Budget Impact Analysis-Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014; 17(1): 5-14. PubMed Abstract | Publisher Full Text
12. Caro JJ, Briggs AH, Siebert U, et al.: Modeling Good Research Practices--Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. Value Health. 2012; 15(6): 796-803. PubMed Abstract | Publisher Full Text
13. Husereau D, Drummond M, Petrosu S, et al.: Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013; 16(2): 231-50. PubMed Abstract | Publisher Full Text
14. Siebert U, Alagoz O, Bayoumi AM, et al.: State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. Value Health. 2012; 15(6): 812-20. PubMed Abstract | Publisher Full Text | Free Full Text
15. Seaton SE, Barker L, Draper ES, et al.: Modelling Neonatal Care Pathways for Babies Born Preterm: An Application of Multistate Modelling. PLoS One. 2016; 11(10): e0165202. PubMed Abstract | Publisher Full Text | Free Full Text
16. Rees CM, Pierro A, Eaton S: Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2007; 92(3): F193-198. PubMed Abstract | Publisher Full Text | Free Full Text
17. Cole CR, Hansen NL, Higgins RD, et al.: Very low birth weight preterm infants with surgical short bowel syndrome: incidence, morbidity and mortality, and growth outcomes at 18 to 22 months. Pediatrics. 2008; 122(3): e573-e582. PubMed Abstract | Publisher Full Text | Free Full Text
18. Panicker J, Scholefield H, Kumar Y, et al.: Atypical chronic lung disease in preterm infants. J Perinat Med. 2004; 32(2): 162-7. PubMed Abstract | Publisher Full Text
19. O’Connor DL, Kiss A, Tomlinson C, et al.: Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1500 g: a randomized clinical trial. Am J Clin Nutr. 2018; 108(1): 108-16. PubMed Abstract | Publisher Full Text | Free Full Text
20. Adams GGW, Bunce C, Xing W, et al.: Treatment trends for retinopathy of prematurity in the UK: active surveillance study of infants at risk. BMJ Open. 2017; 7(3): e013366. PubMed Abstract | Publisher Full Text | Free Full Text
21. Lui K, Lee SK, Kusuda S, et al.: Trends in Outcomes for Neonates Born Very Preterm and Very Low Birth Weight in 11 High-Income Countries. J Pediatr. 2019; 215: 32-40.e14. PubMed Abstract | Publisher Full Text
Overall, this is an important, well-written research protocol. I have some specific comments.

**Background**
1. Paragraph 3/Intervention: Please compare different types of milk used for INDIGO. A table would be useful.

2. Please specify the difference between the context in the US and UK which might lead to the difference between findings from the UK and the US. The justification of literature gaps needs to be clearer.

**Methods**
1. Paragraph 1: Please put the statement of goal at the end of the Background. It will be great to have specific objectives (i.e. to address key components of the studies).

2. Please indicate how each of the three datasets would contribute to the objectives?
   Description of the three data sets upfront and the use of the data. Could be in the form of a table.

3. The data analysis part is based heavily on the data from INDIGO. What about the other two datasets?

4. A diagram to present the two arms of the INDIGO (given this has been done already).

5. Please specify how to estimate the cost before cost-effectiveness or cost-consequence analysis.

6. Why don’t the authors perform a data analysis based on the real data available from the INDIGO? The description of the component cost might need a clearer description.
7. The simulation data analysis could be done at a later stage to show the variation across assumptions.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nutritional Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 18 June 2021

https://doi.org/10.5256/f1000research.24775.r86762

© 2021 Mistry H. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Hema Mistry
Warwick Clinical Trial Unit, Warwick Medical School, University of Warwick, Coventry, UK

In this protocol, the authors want to explore the cost-effectiveness of exclusive human milk diet (EHMD) with routine care for babies born before 30 weeks' gestation. They will do this by building an economic model using available data from a randomised clinical trial, the National Neonatal Research Database, and published literature. The time horizon will be two years. They will adopt a National Health Service perspective and the results will be presented as cost per life year gained. They also aim to do a budget impact analysis, looking at the total cost associated with EHMD compared with current practice.

The protocol was well written and the objectives of the study are well defined. I have a few minor comments to help improve the study:

1. In the Abstract, the authors state that: “the primary outcome for the cost-effectiveness analysis will be incremental cost per life year gained (if observed)”. If this is not observed,
what will the primary outcome be? This needs to be spelt out in the Abstract.

2. In the Abstract, it would also be useful to spell out some of the disaggregated outcomes that you plan to present in the cost-consequence analysis.

3. In the Methods section, the authors say that: "the population will be babies born in England before 30 weeks' gestation", as this aligns with the trial. Technically, babies born before 37 weeks are known as preterm, babies born before 32 weeks are very preterm, and babies born before 28 weeks are extremely preterm. Will the analysis miss out on costs/outcomes if we are excluding babies 31- or 32-weeks' gestation?

4. Would any of the babies after one year of age still be exclusively fed on EHMD diet or would they have cow's milk?

5. In the transition matrix/model, would you not need a separate health state for any outpatient visits/A&E visits etc., seeing as the model cycle length is one day?

6. Are contacts with other health professionals in the hospital, such as hospital dietician, included or excluded?

7. Also, the baby during the first year of life would have contacts with health professionals in the community, such as health visitor or a breastfeeding midwife, are these costs going to be included?

8. Apart from the trial and NHS reference costs, would any other sources be required to get unit cost information?

9. If the baby is included in the study until the age of two and they had a hospital visit between 6 months and 2 years, would they include any other costs of food/solids on top of the milk?

10. In terms of the formula and fortifier costs, would the costs of sterilisers, bottles and teats be included as well?

11. For babies that died, would post-mortem costs be included?

12. I think you need a little more detail on how you will conduct the cost-consequence analysis.

13. Are the any other planned sensitivity analyses apart from the one that was stated in the protocol?

**Is the rationale for, and objectives of, the study clearly described?**  
Yes

**Is the study design appropriate for the research question?**  
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health Economics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com