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Structured lactation support for mothers of very low birthweight preterm infants and establishment of human donor milk banks in German NICUs (Neo-MILK): protocol for a hybrid type 1 effectiveness-implementation cluster-randomised controlled trial

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ABSTRACT

Background Human milk, especially mother's own milk (MOM), is vital for newborns and crucial for very low birthweight (VLBW, <1500 g) preterm infants, who face increased vulnerability. As the production of MOM may be impeded due to preterm birth, it is important to provide lactation support and establish human donor milk (HDM) banks to provide HDM when MOM is fully or initially absent. This protocol describes the design of a study evaluating the effectiveness, implementation and economic aspects of an intervention, which aims to ensure access to MOM or HDM for VLBW infants from the first day of life in German neonatal intensive care units (NICUs).

Methods and analysis The hybrid type 1 effectiveness-implementation cluster-randomised controlled trial, using a stepped-wedge design, will be conducted in 15 level I and level II NICUs across Germany over 26 months. VLBW infants and their mothers will receive either standard care or the Neo-MILK intervention according to the NICU's group status. The primary outcome is the proportion of VLBW infants exclusively fed with MOM at NICU discharge. Secondary outcomes at infant level include feeding patterns, complications, length of stay and frequency of feeding with HDM. Maternal-level secondary outcomes cover lactation/breastfeeding decision and behaviour. A process evaluation and an economic analysis will accompany the study. The data set comprises survey and interview data and routinely collected data from medical records. Statistical analysis will be performed using generalised linear mixed models.

Ethics and dissemination Data collection, storage and analysis comply with current data protection regulations. This study has received ethical approval from the Ethics Committee of the Medical Faculty of the University of Cologne and the local ethics committees of the participating NICUs. Results will be disseminated through peer-reviewed publications and on the project website.

Trial registration number DRKS00025058.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The main strength of the multicentre Neo-MILK project is the hybrid type 1 stepped wedge cluster-randomised controlled trial design with an assessment of both intervention effectiveness and implementation outcomes.
⇒ For evaluation multiple data sources are used, particularly routinely collected data from medical and nursing records of very low birthweight infants, self-reported quantitative and qualitative data from the infants' mothers and professionals working in the participating neonatal intensive care units (NICUs).
⇒ The results will be highly transferable, as the study is highly pragmatic and closely aligned with everyday practice with a large sample size feasible at the infant level.
⇒ A comprehensive process evaluation will be conducted to gain insight into the implementation process, including barriers to and facilitators of implementation, using validated outcome measures.
⇒ Due to the nature of the intervention, neither the participating NICUs nor the majority of the study team will be blinded to intervention allocation.

INTRODUCTION

Mother's own milk (MOM) is of crucial significance for the nascent health trajectory of every newborn. The WHO has been recommending exclusive feeding with human milk (HM) from the first day of life for over two decades.[1] Optimal nutrition is particularly important for vulnerable newborns, such as preterm infants with a very low birth weight (VLBW) of less than 1500 g or newborns with congenital conditions, in order to reduce

mortality and promote infant development.[2–7] VLBW infants fed exclusively with MOM have a reduced risk of conditions such as necrotising enterocolitis (NEC),[8–11] late-onset sepsis,[12] retinopathy of prematurity,[13–15] bronchopulmonary dysplasia (BPD), and experience accelerated growth and improved neurological outcomes.[15 16]

Encouraging mothers to express milk promptly after birth and maintaining a consistent pumping routine is essential for establishing lactation. There is evidence that early initiation within six hours after birth increases the total amount of breast milk available at day 14 postpartum and facilitates an early supply of MOM.[17] This structured promotion of lactation is especially crucial for mothers of VLBW infants, as the production of breast milk might be delayed and impaired.[2] Whenever MOM is not available, human donor milk (HDM) is the preferred alternative to artificially prepared food (formula) for VLBW infants.[18–21] This recommendation is based on both observed benefits for clinical outcomes, such as a significantly lower rate of NEC when MOM is supplemented with HDM instead of formula,[22] and the documented adverse effects of formula feeding on breastfeeding and MOM supply.[23] If infants are initially fed with formula, it is more likely that at the time of discharge they will not be fed with MOM exclusively.[2] Encouraging breastfeeding readiness and structured lactation promotion increases the odds of VLBW infants being fed with MOM when discharged from the neonatal intensive care unit (NICU).[24] Current research also suggests a positive association between the presence of an HDM bank (HDMB), and the rate of infants fed with MOM at the time of discharge, highlighting the processes and changes involved in establishing and operating an HDMB within a healthcare facility, including an increased awareness of the benefits of HM nutrition (MOM and/or HDM) among staff and parents.[25 26]

In Germany, there is currently a lack of structured lactation support for mothers of VLBW infants hospitalised in NICUs, despite the international trend towards evidence-based approaches to promoting lactation and breastfeeding in NICUs[24 27 28] and the availability of initial evidence on the implementation process of lactation programmes.[29 30] Lactation support is provided individually by each NICU and there is evidence that in Germany lactation support is often not adequate and does not comply with evidence-based recommendations.[31]

Similarly, HDM is only available in a limited number of German NICUs due to structural, legal and financial barriers. Of the 211 level I and level II NICUs in Germany, only 40 have established an HDMB.[32] The mode of establishment of these HDMBs varies considerably and has largely relied on the initiatives of dedicated neonatologists. Furthermore, there is no uniform regional distribution, and they are mainly located in large (university) hospitals.[32] In other Western healthcare systems, HDMBs are already established at the national level, with evidence-based frameworks for their implementation, and HDM is more widespread than in Germany.[33–35]

The Neo-MILK project (Structured breastfeeding support and establishment of HM banks in neonatal centres (*Strukturelle Stillförderung und Aufbau von Humanmilchbanken an neonatologischen Zentren*)) was initiated in order to improve access to MOM or, in case of MOM not or not yet being available, HDM for VLBW infants in German level I and level II NICUs. Furthermore, the aim is to promote a more standardised distribution of HDM in NICUs by providing a guideline to establish HDMBs and standardising criteria for which infants receive HDM.[36] The project started in 2021 and was funded by the Innovation Fund of the Joint Federal Committee (funding code: 01NVF19027). In order to improve access to HM in German level I and level II NICUs, the project aims to develop and implement a structured lactation and breastfeeding support programme, explicitly adapted to the needs of parents of VLBW infants in German NICUs. The programme comprises an intervention for delivering structured lactation support and strategies to enhance the implementation of intervention components. In particular, the intervention consists of consultations, information material on pumping, hygienic handling of breast milk, skin-to-skin contact and strategies for solving lactation/breastfeeding problems as well as a web-based app to promote early milk expression, to support mothers during the pumping period and to provide further information to increase mothers' knowledge of lactation/breastfeeding. Additionally, HDMBs will be newly established or expanded in 15 clinics participating in the trial. The development process of these intervention components, which are listed in tabular form in accordance with TIDieR[37] in online supplemental appendix 1, is described in detail elsewhere.[36]

This study protocol describes the design of the hybrid type 1 effectiveness-implementation cluster-randomised controlled trial (c-RCT) evaluating the effectiveness of the Neo-MILK intervention components and its implementation strategies. Furthermore, it outlines how implementation and economic aspects will be examined.

OBJECTIVES

The objectives of this effectiveness-implementation study are to:

1. Compare the effectiveness of the Neo-MILK intervention components and their implementation strategies with the current standard of care (status quo).
2. Develop a better understanding of how different components of the Neo-MILK intervention work, for whom, and under what circumstances.
3. Develop knowledge of how implementation strategies support the delivery of the intervention components.
4. Explore the economic aspects of the intervention and its implementation strategies.

We expect that the Neo-MILK intervention will improve the nutritional status of VLBW infants in terms of exclusive feeding with MOM at the time of discharge (day of discharge) from the NICU (primary outcome), and also

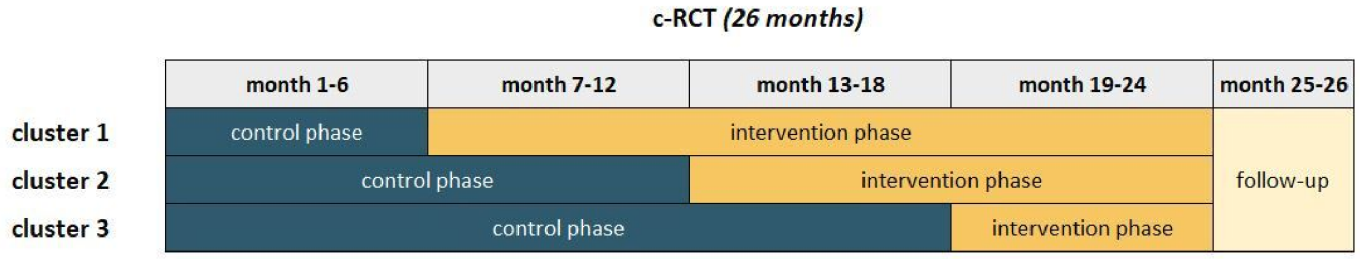

Figure 1 Roll-out including follow-up of the c-RCT in a stepped wedge design. c-RCT, cluster-randomised controlled trial.

improve other outcomes (secondary outcomes at infant level, eg, incidence of complications; and secondary outcomes at maternal level, eg, mothers' pumping or breastfeeding behaviour, and their willingness to donate breast milk). We also expect the results of our evaluation study to inform the wider implementation and the scaling of the intervention.

METHODS AND ANALYSIS

This study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials reporting checklist[38] (see online supplemental appendix 2).

Study design

A multicentre, prospective, hybrid type 1 effectiveness-implementation c-RCT will be conducted in 15 level I and level II NICUs across Germany. The study uses a stepped wedge design. Therefore, all NICUs will start with an initial control period during which none of the NICUs will be exposed to the intervention. Randomisation will take place at ward level. Each of the participating NICUs will be randomly assigned to one of three periods to move from the control period to the intervention period, resulting in three randomised clusters (five NICUs per cluster), as shown in figure 1. The c-RCT will be conducted over a period of 26 months in total. During this time, 24 months will be dedicated to the continuous recruitment of mothers, that is, VLBW infants. An additional 2 months will be devoted to follow up of the last enrolled mother–VLBW infant pair.

To analyse effectiveness and implementation, a stepped wedge c-RCT with the NICU as the unit of randomisation will be used. This design is recommended for hybrid effectiveness-implementation studies and promotes external validity.[39] In the context of the research objective of this study, individual randomisation is neither feasible nor appropriate,[40 41] due to, for example, spillover effects among treated and non-treated individuals in a given NICU. In order to design a more pragmatic study according to the Pragmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2),[42] the evaluation of effectiveness will take place in a real-world NICU setting with limited eligibility criteria. This allows us to study outcomes in typical patients (VLBW infants and their mothers/parents) attending these clinics. The full assessment of the study design using the PRECIS-2 tool can be found in online supplemental appendix 3. The design involves random and sequential crossover of clusters from control to intervention until all clusters enter the intervention phase. Data collection will take place throughout the study, with each cluster contributing observations in both the control and intervention periods.

Setting and trial populations

Study setting

The study will be carried out in 15 NICUs across Germany. Clinics from different federal states, of different sizes, with different ownership structures and with departments relevant to the study, that is, level I and level II NICUs, will be included. Each participating clinic must give its consent by signing a cooperation agreement.

Participants

There will be three groups of participants in this trial:

1. VLBW infants: Preterm infants with a birth weight of less than 1500 g (International Statistical Classification Of Diseases And Related Health Problems, 10th revision, German Modification (ICD-10-GM)): P07.00, P07.01, P07.02, P07.10, P07.11) born in one of the trial clinics during the study period and subsequently hospitalised have to be treated in the NICU of the respective trial clinic. Infants will not be excluded for any reason.
2. Mothers of preterm infants: Mothers aged 18 or older who gave birth to a VLBW infant in one of the trial clinics during the study period.
3. Healthcare professionals (HCPs): Physicians and nurses working at the NICUs concerned.

Recruitment

Recruitment of the NICUs and HCPs

The NICUs will be recruited by applying snowball sampling, stratified by size, organisation and level. The aim is to obtain a diverse sample that includes clinics of different sizes and types. A mandatory precondition is openness towards the topic of HDM and a willingness to promote lactation and breastfeeding.

HCPs will be included both in their role as professionals delivering healthcare and as key informants on the implementation process. Key informants will be identified from NICU staff at trial sites and invited to participate in data collection. In order to survey all HCPs

(complete census), key informants will act as intermediaries between the researchers and the HCPs by distributing survey documents, including written information, to NICU physicians and nurses. Participation is anonymous and voluntary.

Recruitment of VLBW infants and mothers

VLBW infants born between April 2022 and March 2024 who meet the inclusion criteria will be enrolled consecutively in their respective NICUs and will be included anonymously in the collection of routine data without specifically consenting their families. Data for the primary outcome and for secondary outcomes (the proportion of VLBW infants fed with, respectively, MOM only, a mix of MOM and formula, formula only; the occurrence of complications correlated with nutritional status, length of stay and feeding with HDM retrieved from inhouse HDMB) will be obtained from medical and nursing records.

In addition, mothers of VLBW infants will be invited by clinicians to participate in surveys and will receive written information and give their consent for data collection. Participation is voluntary. The following secondary outcomes will be derived from the surveys: pumping or breastfeeding behaviour, breastfeeding/pumping self-efficacy and willingness to donate milk. Further secondary outcomes are specified in the section 'Secondary outcomes'. If mothers are unable to receive the questionnaires (eg, due to language barriers, short hospital stay, infant death or other reasons), this will be documented by the clinician and reported to the researchers. Examples of the consent forms can be found in online supplemental appendix 4.

Randomisation

With the NICU as the unit of randomisation, each of the 15 participating NICUs will be randomly assigned to one of the three clusters in the stepped wedge design. The randomisation schedule will be computer-generated by an independent researcher, who will not be involved in recruitment or intervention allocation. Randomisation results will be reported to the project coordinator and to the respective clinics halfway through the first control period in order to minimise potential contamination. The randomisation list will be stored in a password-protected document to which only study staff involved in the allocation of the intervention will have access. Due to the nature of the intervention, neither the participating NICUs and their HCPs nor the majority of the study team will be blinded to treatment allocation. The investigator performing the statistical analysis of all data collected for evaluation, however, will be blinded to the intervention allocation. In addition, mothers will not be informed of the current status (control or intervention) of their NICU. In economics terms, it is a natural field experiment, in which subjects are not aware that they are participating.[43]

Intervention and control

The complex intervention of Neo-MILK, based on international evidence, aims to ensure that VLBW infants in German level I and level II NICUs have access to HM from the first day of life (MOM and/or HDM). This is to be achieved through (a) the establishment of a structured lactation and breastfeeding support intervention to promote breastfeeding readiness and lactation among mothers of VLBW infants and (b) access to HDM through standardised HDMBs implemented in level I and level II NICUs. To investigate effectiveness, it is essential that only certain intervention components are implemented in the respective phase and that these are completed before moving on to the next phase. The HDMB will be implemented during the last month of each cluster's control phase, and a pool of HDM will be stockpiled to ensure supply from the first day of the intervention period. NICUs entering the intervention phase will participate in a structured implementation programme, which will include standards and procedures for the implementation and integration of the HDMB into healthcare delivery, as well as training for physicians and nurses.

Intervention group

Description of the intervention

VLBW infants who meet the eligibility criteria and who are born during the intervention period at the respective trial clinic will have the opportunity to receive HDM from the first day of life and, if needed, until discharge. In addition, their mothers will receive structured lactation and breastfeeding support to encourage MOM feeding of their infants. This also includes counselling and support for mothers during lactation/breastfeeding. Besides this targeted support after birth (eg, provision of breast pumps and help with expressing milk) already in the prenatal setting, women at risk of preterm birth will, where possible, receive structured information about feeding VLBW infants and about lactation by HCPs.

Due to the emotional and physical stress associated with preterm birth,[44] it is not advisable to address lactation issues for the first time immediately after birth. Therefore, if preterm birth is imminent, the need for early lactation initiation should be discussed prepartum during the consultation with the neonatologist. Prepartum information will be provided during the medical consultation, aimed at providing knowledge, initiating commitment to MOM and HDM feeding, promoting a positive attitude towards breastfeeding and providing emotional support to the expectant mother. In the case of an unexpected birth, information will be provided to mothers/parents after the VLBW infant has been admitted to the NICU. This will be followed by instruction on how to use a breast pump, along with regular reminders to initiate early lactation within the first 6 hours after birth in order to promote early feeding with MOM.[17] HCPs remain the point of contact for any lactation problems.[45] The various intervention components are listed in tabular form in accordance with TIDieR[37] in online supplemental appendix 1.

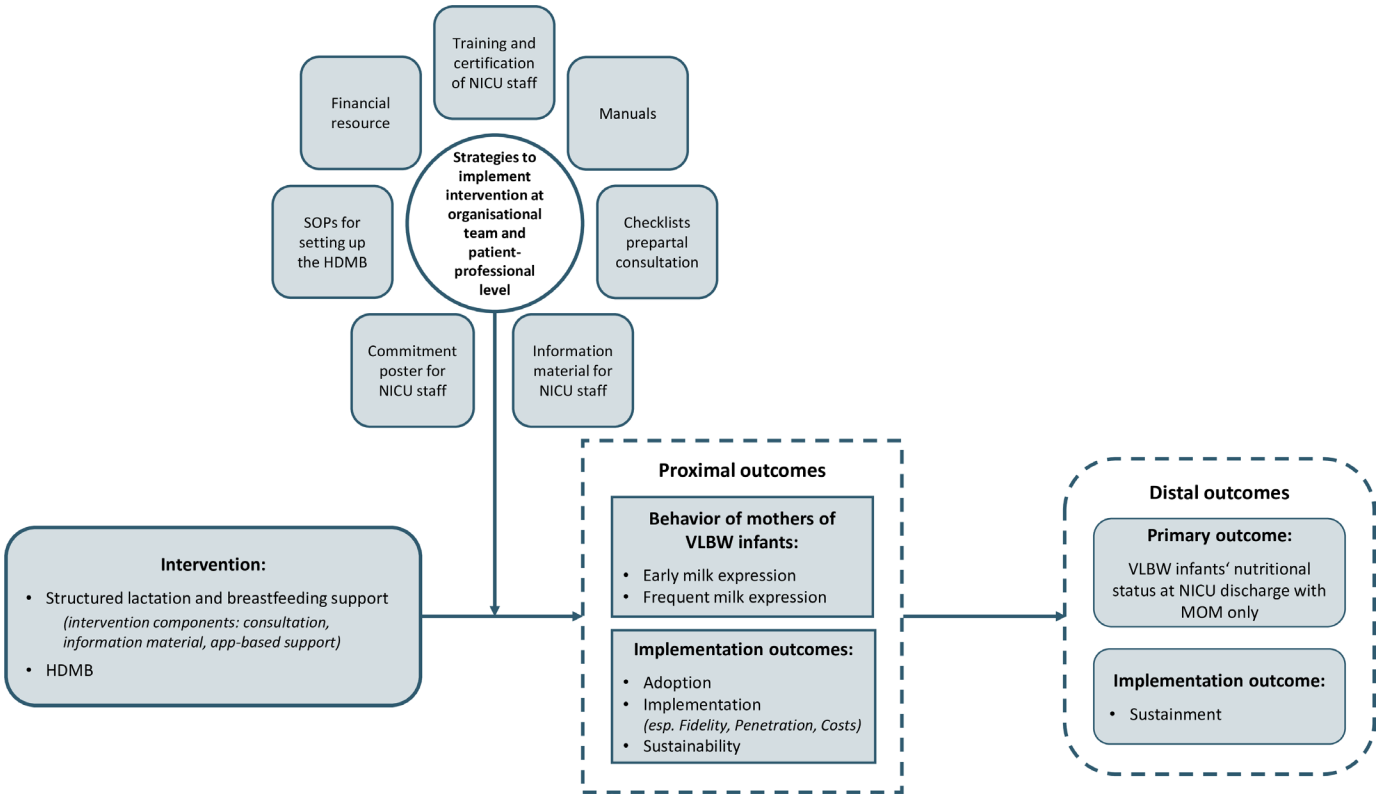

Figure 2 Lactation and breastfeeding support programme and outcomes to be evaluated. HDMB, human donor milk bank; MOM, mother's own milk; NICU, neonatal intensive care unit; SOP, standard operating procedure; VLBW, very low birth weight.

Implementation of the intervention

The implementation of the intervention will be supported by different implementation strategies, identified during the intervention development phase and specified as suggested by Proctor *et al*[46] (see online supplemental appendix 5). These are based on the evidence in the literature and two mixed-methods surveys (qualitative and quantitative). Mothers of VLBW infants, senior NICU physicians/nurses and members of HDMB management were surveyed.[36] In addition to infrastructural strategies to set up the HDMBs, these implementation strategies will include video-based training sessions for nursing and medical NICU staff, instructions on how to communicate advice to mothers, guidelines and checklists for the structured and standardised provision of evidence-based information, tools providing commitment nudges for both medical staff and mothers, that is, parents, and information material both on paper and app-based for parents on the topics of pumping, breastfeeding and alternative nutrition for infants (eg, HDM, formula). The initial programme theory, which contained a theory of change,[47] will be refined and serve as a basis for interpreting the results and thus contribute significantly to explaining the observed intervention effect. Figure 2 shows the lactation and breastfeeding support programme and the proximal and distal outcomes to be evaluated.

Control group

The control group will receive care according to the respective NICU's current standards. However, it cannot be ruled out that HDM may be provided as part of this standard care process during the control period and/or that the mothers receiving support may be following a lactation intervention overlapping with the one developed for our study.

Measures and outcomes

Primary outcome

The primary outcome for evaluating the effectiveness of the lactation and breastfeeding support programme is the proportion of VLBW infants fed exclusively with MOM on the day of discharge from the NICU. There is no specific time point for measurement on the day of discharge from the NICU. Data for the primary outcome will be collected from medical and nursing records.

Secondary outcomes

Secondary outcomes based on medical and nursing records at VLBW infant level are the proportion of VLBW infants fed with, respectively, MOM only, a mix of MOM and formula, formula only; the occurrence of complications correlated with nutritional status (NEC, BPD, early-onset sepsis (occurring within the first 3 days of life) and late-onset sepsis (occurring between the day of life 4 and 120))[27 48 49]; length of stay[50] and feeding with HDM retrieved from inhouse HDMB. The routinely collected data will be supplemented by surveying mothers at specific time points (t_0=4 weeks postpartum, t_1=8 weeks postpartum) using standardised questionnaires, which were developed with reference to validated instruments.[19 20 22]

At maternal level, the following secondary outcomes will be derived from the surveys: pumping or breastfeeding behaviour, breastfeeding/pumping self-efficacy and willingness to donate milk. In addition, other components such as the willingness to accept HDM for their infant and the amount of milk pumped, as well as an assessment of the intervention components, will also be included in the survey. To investigate the use of HDMBs, the data on HDM distribution by HDMBs will be analysed (in particular: the number of potential donors (mothers who have preterm birth at the respective NICU and meet medical eligibility criteria), actual donors, milk volume (donated and fed) and number of children who received milk).

Data collection and management

Data collection

Data on primary and secondary outcomes at infant level will be collected from medical and nursing records during both control and intervention periods (24 months, April 2022 to March 2024) as well as during the follow-up (2 months, April 2024 to May 2024). A standardised case report form (CRF) will be developed in preparation for data extraction. Quarterly data will be provided anonymously by participating NICUs. To investigate secondary outcomes, pseudonymised data will be collected from written questionnaires at maternal level, after informed consent has been obtained from the mother. Paper-based questionnaires will be provided to mothers by NICU staff. After completing the questionnaire, mothers will return it by post to the University of Wuppertal, where it will be recorded and entered into the database. No reminders will be sent to remind mothers to participate in data collection.

Data management

The database will consist of routinely collected data extracted from medical and nursing records, and quantitative and qualitative data from surveys and interviews. The collection of personal information is unavoidable for the evaluation of the intervention components. Data will be collected, stored and processed for this purpose. To ensure data protection, a data protection policy in accordance with European and German data protection law will be developed with the project partners. In scientific activities, the principles for ensuring good scientific practice of the German Research Foundation will be applied at all times.[50]

Sample size

To analyse the primary outcome, information on the nutritional status of VLBW infants at the time of discharge from the NICU will be collected using a standardised CRF over a period of 26 months. In line with the current literature[51] and based on a contextual analysis carried out during study planning, the sample size is calculated on the assumption that a baseline of 30% of VLBW infants are fed exclusively with MOM at the time of discharge prior to the start of the trial. Assuming an increase in prevalence by a factor of 1.7 (α=0.05, β=0.20, intracluster correlation coefficient (ICC)=0.05), a total of 12 clusters (NICUs) are needed, with an average cluster size of 40 VLBW infants per year (80 VLBW infants for a study duration of 24 months). Therefore, a total sample size of at least 960 VLBW infants is required for both the intervention and control groups (480 per group; calculated using the R package swCRTdesign, version 3.1, swPwr). Similar effects have been reported in international trials.[51] We aim to recruit 15 NICUs to account for organisational drop-outs. The risk of drop-out in VLBW infants will be minimal as the primary outcome data will be collected through medical and nursing documentation.

Statistical methods

To assess effectiveness, the primary analysis strategy will include all preterm infants admitted to one of the participating NICUs who meet the inclusion criteria. The primary outcome will be assessed at VLBW infant level. The primary statistical analysis will be conducted as an intention-to-treat (ITT) analysis using the nutritional status of the VLBW infants at discharge from the NICU as the dependent variable in a generalised linear mixed model (GLMM).[52] The multilevel structure will be accounted for by fixed time effects and random effect for NICUs. The intervention effect will be tested using α=0.05. To analyse secondary outcomes, an explanatory analysis approach will be used. The robustness and validity of the results will be assessed using sensitivity analyses, which will be performed for different subgroups, for example, infants with a birth weight below 1000 g or a CRIB score greater than 10. Missing data for the primary outcome will not be imputed. For all further analyses, missing data will be imputed using multiple imputation by chained equations. An interim analysis will not be conducted.

Process evaluation

To understand the effects of the Neo-MILK intervention and its underlying mechanisms, implementation processes, and contextual influences, a comprehensive process evaluation will be conducted alongside the c-RCT.[45–47] The process evaluation will be theoretically informed by the theory of planned behaviour,[53] normalisation process theory (NPT),[54] the consolidated framework for implementation research (CFIR)[55 56] and determinants of implementation effectiveness.[57] In addition, as we aim to refine and consolidate the initial programme theory, some parts of our process evaluation are consistent with realist principles. Realist evaluation as a theory-driven methodology seeks to facilitate an in-depth understanding of how and in what circumstances complex interventions work.[58]

A mixed-methods approach (quantitative: standardised questionnaires; qualitative: interviews, document analysis, discussion groups) will be used at different levels (mothers of VLBW infants, NICU HCPs and organisation) to collect data throughout the c-RCT.[59] Data will be collected on the following topics: context, recruitment,

delivery of the intervention and the implementation strategy, as well as recipients' reasonings, implementation work and its determinants, and implementation outcomes. The timing of data collection at NICU level will be determined by the NICU's assignment to one of the three cluster groups. Quantitative data at HCP level will be collected anonymously via written questionnaire. Interviewees (mothers and NICU key informants) can choose to be interviewed by video call or telephone, while discussion groups (with key informants from all participating NICUs) will be held by video call after consent has been obtained. Several dates will be proposed for organising the discussion groups so as to ensure in-depth discussion in small groups between representatives of the NICUs from different clusters. Both interviews and discussion groups will be audio recorded and transcribed. In addition, field notes will be collected throughout the c-RCT, starting with the overall introduction of the intervention, to assess the (initial) implementation process and the degree of implementation in daily practice. These documents may encompass a variety of materials, such as training protocols and the clinics' implementation guidelines. NICUs will provide copies to the researchers for review or grant access for data extraction. An overview of planned data collection within the process evaluation is shown in online supplemental appendix 6.

All process evaluation data will initially be analysed descriptively and exploratively. Qualitative data material will be analysed by combining a broadly deductive analytical approach with an inductive analysis to explore new findings related to the specific intervention and contexts. The method of document analysis will also help identify barriers to or facilitators of the implementation process. Data management will be supported by NVivo (V.15). For the purposes of realist evaluation and to gain more explanatory depth, we will use a multiple-embedded case study design[60] and define each of the 15 NICUs as a single case that we will follow throughout the c-RCT. For each NICU, case study and cross-case analyses will be conducted. Cross-case analyses serve to refine specific mechanisms and outcomes induced by intervention components in a specific context (context–mechanism–outcome configurations). This will allow us to obtain knowledge of intervention components that were not implemented in a specific context or failed to induce the intended behaviour or intended outcome. Researchers will then explore possible reasons and mechanisms for the differences found between different contexts, in order to understand general patterns.

Analysis of economic aspects

The analysis of economic aspects is intended to contribute to estimating (1) intervention costs from the healthcare provider perspective and (2) implementation costs. In addition, (3) expenses incurred by mothers/parents will be taken into account, as these can affect the acceptability of the intervention.

1. Intervention costs: Time-driven activity-based costing[61] will be used to determine intervention costs per patient.
2. Implementation costs: The implementation costs will be determined in several steps, analogous to the intervention costs. As a first step, qualitative interviews with key informants will be conducted to identify the components of the implementation processes and the use of resources for each step in the implementation process. Based on the results of the interviews, as a second step, a standardised (postal) survey will be developed, which will record institution-specific expenditure for implementing the Neo-MILK intervention.
3. Out-of-pocket costs to mothers: In addition, out-of-pocket costs to mothers for remedies and aids as well as any outpatient physician and private lactation consultations, and medication connected to the intervention will be included in the analysis. These costs will be recorded by the mothers using standardised questionnaires.

Ethics and dissemination

This project has received ethical approval from the Ethics Committee of the Medical Faculty of the University of Cologne, No. 21–1506, from the Ethics Committee of the University of Wuppertal, No. 211007, and from the ethics committees responsible locally for participating clinics. In case of important modifications to the protocol, the aforementioned Ethics Committees and the funding institution will be informed immediately.

HCPs and participants receive full information about the study before they participate in data collection. HCPs will collect routine data as part of their ordinary duties but are free to participate or not in staff surveys. Data collection can be stopped at any time if the staff member so wishes.

Written informed consent will be obtained from all participating mothers. Any participating mother may withdraw her consent at any time.

Study results will be published in a peer-reviewed, MEDLINE-listed journal. A German website (https://neo-milk.uni-koeln.de/) was created to provide study materials and to publish study results at a later stage.

Patient and public involvement

Patients and the public were not involved in the trial's design, management or conduct. Mothers and parents of preterm infants were involved in the development of the intervention and piloting of instruments (questionnaires and interview guidelines).

DISCUSSION AND LIMITATIONS

The present study investigates the effect of a structured lactation and breastfeeding programme combined with the implementation of HDMBs in German level I and level II NICUs on the rate of VLBW infants being fed exclusively with MOM when discharged from

the NICU. The programme is directed at mothers of VLBW infants as well as NICU HCPs. The method used is a multicentre, prospective, hybrid type 1 effectiveness-implementation c-RCT with a stepped-wedge design, to examine both effectiveness and implementation. In the intervention phase, VLBW infants will be offered the opportunity to receive HDM from the first day of life, if MOM is absent or not available in sufficient quantity, and their mothers will be supported according to the developed structured lactation and breastfeeding support programme. The control group will receive care according to respective NICU standards.

Routinely collected data for the primary outcome is guaranteed, as there is no requirement to obtain consent for the analysis of anonymous and coarsened data extracted from medical and nursing records. Therefore, with a calculated sample size of at least 960 infants, the transferability of the results is expected to be high. This assumption is supported by the rather pragmatic/pragmatic study design as assessed by the PRECIS-2 tool. Compared with other studies evaluating breastfeeding interventions,[62–64] we found lower scores on the pragmatic–explanatory continuum (see online supplemental appendix 3). In addition, we found that implementation aspects were not considered during the design of the intervention. This study has limitations. As organisational and structural changes are being addressed, blinding is not possible. Due to the emotional stress associated with preterm birth,[44] mothers may not feel comfortable participating in surveys and interviews. In addition, language barriers may also reduce the response rate, as the questionnaire will only be available in German. Nevertheless, we expect a response rate of around 30% for secondary outcomes. A further limitation is the absence of a predetermined time point for the measurement of the primary outcome on the day of discharge from the NICU. This is attributable to the objective of conducting a very pragmatic study that is in close proximity to everyday care, in which discharge times can vary across the various NICUs and VLBW infants.

An increase in the number of VLBW infants fed with MOM at discharge from the NICU and relevant changes in secondary outcomes are expected. International publications support these hypotheses.[8 64 65] The comprehensive process evaluation will contribute to a deeper understanding of how different components of the Neo-MILK intervention work, and for whom and under what circumstances, and how implementation strategies support the implementation of the intervention components. It is expected that the results of the study will contribute to improving the current standard of care for VLBW infants and their mothers. Based on the results of this evaluation, a recommendation to induce the intervention as a new standard of care in all German level I and level II NICUs may be derived.

Duration of the project

Neo-MILK started in January 2021 and should be completed by December 2024. The c-RCT started in April 2022. Data will be archived for 10 years after completion of the study.

Trial status

NICU recruitment began at the project's start in January 2021, with only level I NICUs being enrolled. Patient enrolment began in April 2022, at the start of the c-RCT. The last patient will be included at the end of March 2024, and the 2-month follow-up will accordingly be completed at the end of May 2024. Data collection for primary and secondary outcomes will be completed by the end of June 2024. Analyses of primary and secondary outcomes will be completed in December 2024.

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