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Complete List of Authors:	Laborie, Sophie; Hospices Civils de Lyon, Neonatology Denis, Angelique; Hospices Civils de Lyon, Université de Lyon Horsch, Antje; University of Lausanne, Institute of Higher Education and Research in Healthcare; Lausanne University Hospital, Woman-Mother-Child Occelli, Pauline; Hospices Civils de Lyon, Pôle IMER; Université de lyon Margier, Jennifer; University Hospital Centre Lyon, public health Morisod Harari, Mathilde; Centre Hospitalier Universitaire Vaudois, Child and Adolescent Psychiatry Claris, Olivier; Hospices Civils de Lyon, Hopital Femme Mère Enfant, Neonatology; Université Claude Bernard Lyon 1, Equipe P2S4129 Touzet, Sandrine; Hospices Civils de Lyon, Pôle IMER; Université de Lyon, Laboratoire Health Services and Performance Research (HESPER) EA 7425 Fischer Fumeaux, Celine; University Hospital of Lausanne, Woman-mother-child
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Breastfeeding peer counselling for mothers of preterm neonates: protocol of a stepped-wedge cluster randomized controlled trial.

Sophie Laborie[a], Angélique Denis[b], Antje Horsch[c,d], Pauline Occelli[b], Jennifer Margier, Mathilde Morisod Harari[f], Olivier Claris[a,g], Sandrine Touzet[b,h], Céline J. Fischer Fumeaux[c].

Affiliations: [a]Hospices Civils de Lyon, Service de Réanimation Néonatale et Néonatologie, Hôpital Femme Mère Enfant, Bron, France; [b]Hospices Civils de Lyon, Pôle Santé Publique, Service recherche et épidémiologie clinique, Lyon, France; [c]Lausanne University Hospital, Clinic of Neonatology, Department Woman-mother-child, Lausanne, Switzerland; [d]Institute of Higher Education and Research in Healthcare, University of Lausanne, Lausanne, Switzerland; [e]Hospices Civils de Lyon, Pôle Santé publique, Service Evaluation Economique en Santé; [f]Lausanne University Hospital, Service of Child and Adolescent Psychiatry, Lausanne, Switzerland; [g]Université Claude Bernard, Equipe P2S4129, Lyon, France ;[h] Université Claude Bernard Lyon 1, HESPER EA 7425, Lyon, France

Acronym : Alaïs

Correspondance to: Sophie Laborie, Service de Néonatologie et Réanimation Néonatale, Hospices Civils de Lyon - Hôpital Femme Mère Enfants, 59, Boulevard Pinel - 69677 Bron, France, [sophie.laborie@chu-lyon.fr], tel. +33 (0)4 27 85 52 84, fax +33 (0)4 27 86 92 27

Mail of co-authors: Celine-Julie.Fischer@chuv.ch, angelique.denis@chu-lyon.fr, olivier.claris@chu-lyon.fr, sandrine.touzet@chu-lyon.fr, Jennifer.margier@chu-lyon.fr, pauline.occelli@chu-lyon.fr, Antje.Horsch@chuv.ch, Mathilde.Morisod@chuv.ch

Keywords: randomized controlled trial, preterm infants, breastfeeding, peer counsellors, human milk

Trial registration: clinicaltrials.gov NCT03156946 see trial registration data set on table 1

Table 1: trial registration: data set

Data category	Information
Primary registry and trial identifying number	clinicaltrials.gov NCT03156946
Date of registration in primary registry	May 2, 2017
Secondary identifying numbers	69HCL17_0033
Source(s) of monetary or material support	*Programme de Recherche sur la Performance du Système de soins* (PREPS 16-0373), *Direction de l'Hospitalisation et de l'Organisation des Soins* ; Fondation Planètes Enfants Malades, Fondation Lotty Buol
Primary sponsor	Hospices Civils de Lyon, Direction de la recherche Clinique et de l'Innovation, <cecile.gayet@chu-lyon.fr>
Secondary sponsor(s)	NA
Contact for public queries	Sophie.laborie@chu-lyon.fr
Contact for scientific queries	Sophie.laborie@chu-lyon.fr
Public title	Evaluation of a Peer Counseling Breastfeeding Support Program for Mother-preterm Infant Dyads (Alaïs)
Scientific title	*Supporting Breastfeeding for Preterm Infants by Peer Counselors: a Cluster Randomized Controlled Trial*
Countries of recruitment	France, Switzerland, Belgium
Health condition(s) or problem(s) studied	Breastfeeding and prematurity
Intervention(s)	intervention: *breastfeeding mother-to-mother support from the hospitalization in the maternity and NICU up to 1 month after discharge*
	control: receive the usual care
Key inclusion and exclusion criteria	Inclusion Criteria: any infant born <35 weeks' gestation, hospitalized in NICU before 24 hours old and younger than 168 hours (7 days) old.
	Exclusion Criteria: infant with fetal malformation that is life-threatening infant with medical contraindication for breastfeeding parent(s)' non-consent to be involved in the study

Data category	Information
	mother with prolonged medical contraindication for breastfeeding mother with psychiatric disorders making breastfeeding support impossible if no communication is possible with the mother if the level of communication with the mother does not allow breastfeeding support, with or without a third party
Study type	Interventional Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Supportive Care
Date of first enrolment	November the 5th, 2018
Target sample size	2400
Recruitment status	Recruiting
Primary outcome(s)	Breastfeeding continuation rates at corrected postnatal age of 2 months
Key secondary outcomes	Breastfeeding rates at 6 months of corrected age Breastfeeding duration Neonatal severe complications Death rates at 36 weeks of corrected age Infant temperament Mother-Infant bonding Mother Anxiety, Depression, Posttraumatic stress Disability rate at corrected postnatal age of 24 months Costs effectiveness [up to first two years of life] Feasibility of the breastfeeding support program Acceptability of the breastfeeding support program

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ABSTRACT

Introduction Among preterm infants, mother's own milk feeding reduces neonatal morbidities and decreases the length of hospital stay. However, breastfeeding rates and duration are lower than among term infants and there is a need for efficient support. Peer counselling is effective in increasing breastfeeding in term infants.

We aim to investigate whether peer counselling may be a feasible and effective breastfeeding support among preterm infants.

Methods and analysis Eight European centres will participate in this stepped-wedge cluster randomized controlled trial. We plan to include 2400 hospitalized neonates born before 35 gestational weeks. Each centre will begin with an observational period. Every three months, a randomized cluster (centre) will begin the interventional period with peer counsellors until the end of the study. The counsellors will be formed and supervised by trained nurses. They will have a weekly contact with participating mothers, with a face-to-face meeting at least once every 15 days. During these meetings, peer counsellors will listen to mothers' concerns, share experiences, and help the mother with their own knowledge of breastfeeding.

The main outcome is breastfeeding rate at 2 months of corrected age. Secondary outcomes are breastfeeding rates at hospital discharge and at 6 months, breastfeeding duration and neonatal morbi-mortality. Mental health of the mother, mother-infant bonding, and infant behaviour will be assessed using self-report questionnaires. A neuro-developmental follow-up and a cost-effectiveness analysis and a cost-consequence at 2 years of corrected age will be performed among infants in a French subgroup.

Ethics and dissemination French, Belgian and Swiss ethics committees gave their agreement. Publications in peer-reviewed journals are planned on breastfeeding, mental health and medico-economic outcomes.

Trial registration number: NCT03156946

ARTICLE SUMMARY

Strengths and limitations of this study

- This study is the first multi-centre and multi-national randomised trial investigating the efficacy of peer counsellors to support and improve breastfeeding of preterm infants.
- This study gives us the opportunity to test the feasibility of such an intervention in Europe.
- The potential effect of peer counselling on maternal mental health and mother-infant bonding will also be investigated.
- The cost consequence analysis and the cost-effectiveness ratio expressed as the cost by avoided impairment at 2 years of corrected age will be calculated for a subgroup of infants from a French geographic region.
- The measurement of psychological outcomes is limited by the use of self-report questionnaires.

INTRODUCTION

According to a recent meta-analysis, increasing breastfeeding rates according to Word Health Organization recommendations could prevent yearly more than 800 000 deaths of children below the age of 5 years [1] and could save more than 300 billions of dollars per year.[2]

Prematurity represents the leading cause of infantile mortality around the world, and can lead to short- and long-term severe complications. In preterm neonates, mother's own milk feeding is associated with a significant decrease of severe morbidities, such as sepsis,[3-6] enterocolitis,[3,6,7] retinopathy of prematurity,[8] and bronchopulmonary dysplasia.[9]. It has been shown to reduce hospital stay durations, as well as the risk of re-hospitalisations.[10] Breastfeeding is also associated with a dose-dependent increase of neuro-developmental scores in infancy and childhood.[11,12] However, studies have shown that breastfeeding rates of preterm infants at hospital discharge are far below those of term infants.[13]

In term infants, peer counselling by mothers with a previous positive experience of breastfeeding is effective in promoting breastfeeding, including among low income families[14], and is advocated by the World Health Organization.[15] In neonatal intensive care units (NICUs), support by "veteran" parents with previous comparable experiences supporting NICU parents can have important benefits in term of psychological health for the parents, such as reduced stress, anxiety and depression, and increased perceived social support.[16] So far, studies on breastfeeding peer support in NICUs are scarce. A small American randomized trial showed a significant increase in breastfeeding at 12 weeks postpartum in the group with peer counsellors.[17] Furthermore, the beneficial effect of peer support in NICUs increased even further by the co-intervention of a breastfeeding consultant,[18] as already demonstrated for full-term infants.[19]

This multi-center randomized cluster trial aims to study the effect of breastfeeding peer counselling for mothers of preterm neonates. Our primary objective is to assess breastfeeding rates among preterm neonates at 2 months of corrected age. Our secondary objectives are to assess breastfeeding rates at hospital discharge and at 6 months, breastfeeding duration, and neonatal morbi-mortality. Furthermore, psychological consequences of the breastfeeding counsellors' intervention on maternal mental health, mother and child bonding, and infant behaviour will be investigated. Moreover, we aim to assess satisfaction with the peer breastfeeding support and to measure its implementation. A neuro-developmental follow up and a cost-effectiveness analysis at 2 years of corrected age will be performed among infants in a French subgroup. Finally, the efficiency and the feasibility of such a peer support system for preterm breastfeeding support in different European countries will be assessed.

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METHODS

Design and setting

A stepped wedge cluster randomized controlled design with repeated cross-sectional samples will be used. This design was chosen to prevent contamination of the intervention in the centre and to allow to deliver the intervention to all participating centre.

Each participating centre will correspond to a cluster, with: i) an observational (or control) period, ii) a 3-month transitional period and iii) an intervention period. The trial will thus have 9 waves, staggered by 3 months, as shown in Figure 1. All clusters will start with the control situation at the beginning of the study. At each time step, a new cluster will cross over from the control period to the transition period and 3 months later to the intervention period.

The order of implementation is randomized based on a computer-generated random sequence performed by an independent researcher. Due to the nature of the intervention it is not possible to blind mothers and teams in NICUs.

During the transition period, the centres do not contribute to analysis. This transition period takes into account the time it takes for the recruitment and the training of peer counsellors (Figure 1).

The trial is conducted in 8 NICUs, of which 6 are in France, one in Switzerland and one in Belgium. One of the French centres is located in the overseas territory of France.

In each centre, two specialist lactation nurses or lactation consultants will supervise the peer support intervention. All supervisors participate in an identical 5-day training period, enabling them to recruit, train and supervise counsellors. This training is provided by an organization (Association Relai Parentalité Allaitement), which has experience in training breastfeeding counsellors in neonatology.

Inclusion and exclusion criteria:

The mother and child dyads can be included if:

- Mothers:
    - Deliver before 35 weeks of gestational age, and
    - Have sufficient French skills to adequately participate in the study, and
    - Give their informed consent before 7 days following delivery
- Neonates:
    - Are admitted in a neonatal unit in the first 24 hours following birth
- Mothers and neonates: do not present medical counter-indications to breastfeeding

Serious mental disorder in mothers (contraindicating peer counselling) and life threatening congenital malformations in infants constitute exclusion criteria.

Eligibility of peer counsellors

Peers counsellors will be eligible if they had breastfed at least one preterm infant hospitalized in a NICU, if they had a positive experience of breastfeeding, and if the breastfed child is in good health. They will be interviewed and selected by the supervisors and participate in a 20-hours training program led by the supervisors. They are volunteers, and will not be paid even if indemnities will partially be covered, as well as their travel or phone costs.

Control period

The mothers will receive professionally available breastfeeding support in each NICU (usual care). The organization of this support depends on NICUs with various combinations and levels of support by nurses and/or by breastfeeding consultants. In the Swiss centre only, an additional peer support on a weekly basis with a group meeting will also be proposed during both the intervention and control periods, as this collective peer support system was already in place before the study. After discharge, the mothers are supported by the nurses from the "Protection Maternelle et infantile" in France., by pediatric nurses, and by independent midwifes in Switzerland and in Belgium.

Intervention period

Additionally to existing professional lactation support mothers will receive an individual peer support by one of the peer counsellors.

Peer counselors will visit mothers first either in the obstetrical unit before birth whenever possible in case of premature delivery risk, or in the NICU. Then, during the NICU stay, at least weekly contact between peer counselors and participating mothers (face to face, visio-

phone or call) will be planned, with a face-to-face meeting weekly or at least once every 15 days.

After infant discharge from the NICU, or if the infant is transferred to another hospital, the weekly contact will continue by phone until 1 month after the infant's return to parental home.

During these meetings, peer counsellors will listen to mothers' concerns, share experiences, and help the mother with their own knowledge of breastfeeding.

The peer breastfeeding support is planned to stop in case of weaning or one month after home discharge, whatever come first. If the mother or the counselor asks for discontinuation, another counselor will be proposed to participating mothers.

Premature discontinuation of the study will arrive in case of infant or maternal death or parental withdrawal of their consent. In those cases, infants will be followed up until the end of the study period, except if the parents refuse it.

Outcomes and measures

- Primary outcome and measure

The main outcome is breastfeeding rate at 2 months of corrected age. An infant who received the mother's own milk during the preceding 48h will be considered as breastfed.

- Secondary outcomes and measures

  All measures and their timings are listed in Table 2.

Table 2: Measures and timing

	15 days	30 days	discharge	2months	6 months	24 months
Breastfeeding (exclusive or mixed)			x	x	x	
Neonatal mortality and morbidity			x			
Neurodevelopment and sequelae						x
Psychological assessment	x	x			x	
Satisfaction of parents				x		
Economic costs	x	x	x	x	x	x

- *Breastfeeding*

Breastfeeding initiation is defined as receiving at least once the mother's own milk. Breastfeeding at discharge is defined as receiving some mother's own milk either directly, with a bottle or a tube during the 48 hours before the NICU discharge. Breastfeeding at 6 months of corrected age is defined as receiving any mother's own milk in the 48h before 6 months corrected age. Exclusive breastfeeding is defined as receiving no other milk or food than mother's own milk during the 48 hours before discharge, 2 and 6 months corrected age. Duration of breastfeeding is defined as duration from birth until last administration of mother's own milk. If breastfeeding is continuing at 6 months of corrected age, the longer duration will not be record (data censored).

- *Neonatal mortality and morbidity*

Mortality and the following complications will be assessed during hospitalization until 36 weeks of corrected age: intra ventricular haemorrhage (grade > 2),[20] periventricular

leukomalacia, enterocolitis stage > 1,[21] bronchopulmonary dysplasia defined as a persistent oxygen dependency or respiratory support at 36 weeks corrected age,[22] persistent ductus arteriosus necessitating a treatment, retinopathy of prematurity grade > 2,[23] sepsis (proven or probable).[24]

- *Neurodevelopmental outcomes*

In infants born below 33 weeks gestational age or with a weight below 1500g living in a specific geographic French area (Rhône, North of Isère, Drome, Ardèche), the neurodevelopment will be assessed at 24 months corrected age with the Brunet Lezine scale.[25] The number of cerebral palsy, deafness, blindness, developmental delay (DQ below 85) will be recorded in the same population.

- *Psychological outcomes:*
  - *Mothers*

Various mental health symptoms of the mothers will be assessed using several validated self-report questionnaires. The questionnaires will be completed by mothers reading French fluently.

i. Depressive symptoms in the last 7 days will be measured 15 days after inclusion and at 6 months corrected age with the Edinburgh Postnatal Depression Scale (EPDS),[26], which has been validated for pregnant women[27] and in a French sample, with good psychometric properties.[28]

ii. Anxiety symptoms will be assessed 15 days after inclusion and at 6 months corrected age with the Hospital Anxiety and Depression Scale (HADS), validated in French, with good psychometric properties.[29-31] The anxiety subscale has 7 items measuring state-anxiety in the last 7 days. It may be used as a measure of symptom severity.

iii. Mother-infant bonding will be measured using the Mother-Infant-Bonding Scale (MIBS),[32,33] 15 days after inclusion and at 6 months corrected age. In this questionnaire, the mother rates eight adjectives describing her feelings toward her infant that are indicative of mother-infant bonding.[32,33] This questionnaire was translated into French.[34]

iv. Maternal posttraumatic stress disorder symptoms will be assessed 1 month after childbirth and at 6 months corrected age using the Posttraumatic Checklist for DSM 5 (PCL-5).[35,36] This questionnaire has 20 items, measuring the 20 DSM-5 symptoms of posttraumatic stress disorder (PTSD). It was translated into French and can also be scored to provide a provisional PTSD diagnosis.

v. Parenting stress will be evaluated at 6 months corrected age with the French version of the Parenting Stress Index Fourth Edition Short Form (PSI-4 SF),[37], which has 36 items assessing parental distress, dysfunctional parent-child interactions, and child difficulties. The PSI has good psychometric properties.[38]

Satisfaction of the mothers regarding the breastfeeding support and the intervention will also be assessed with a questionnaire designed for the study.

- *Infant behaviours*

Infant behaviour will be measured at 6 months of corrected age with the French version of the Infant Behaviour Questionnaire – Revised (IBQ-R) Very Short Form.[39] The mother reports on a 7-points Likert scale the frequency of her infant's behaviours during the previous two weeks.[39]

- *Peer counselors*

Depressive symptoms will be measured with the EPDS,[26,28] The satisfaction of peer counsellors will be measured with a questionnaire designed for the study.

- *Fathers*

The satisfaction of father on the intervention will be evaluated with a questionnaire designed for the study.

- *Economic outcomes*

Cost data during the two first years will be gathered on a sub-population of infants included by Rhône-Alps region centres. To assess the total cost of each group, the number of resources consumed (consultations, hospitalization, drugs, medical devices…) will be extracted from the regional healthcare database completed by a direct collection by the parents for additional costs (not covered by medical health service).

The primary medico-economic endpoint will be the incremental cost-effectiveness ratio (ICER) at 2 years of corrected age for intervention group versus control group. It will be expressed as incremental cost per impairment avoided. This outcome will be measured in a subgroup of infants born below 33 weeks gestational age or below 1500g from a precise geographic region from Rhone Alps.

The secondary medico-economic endpoint will be the cost-consequence analysis at 2 years of corrected age. The health outcomes considered will be the mortality and the hospitalisations rate.

- *Feasibility of the intervention*

The implementation of the intervention will be reported: number and characteristics of counsellors (age, place of birth, study level, parity, age of the previous preterm child), number of face-to-face meetings and of Skype or phone contacts, duration and subjects treated in the meetings.

The proportion of mothers declining peer support counselling will be measured with the reason for refusal. The duration of counselling and the proportion of mothers ending the peer counselling prematurely and their reasons will also be assessed.

- *Healthcare satisfaction*

The satisfaction and the acceptability of the intervention by healthcare professionals (medical doctors and nurses) will also be evaluated by specific questionnaires developed for the study.

Blinding

Owing to the nature of the intervention, healthcare providers, parents and researchers will not be blinded to the intervention phase.

Other changes occurring in the NICU during the study period

All events, such as organizational modifications that occur during the study period and may interact with the intervention or the study results will be recorded in a logbook.

Study sample size

We calculated the sample size for the stepped-wedge trial using the method of Hussey and Hughes.[40] The trial was designed with 8 clusters and 9 time periods (Figure 1) with 3 transition periods between control and intervention periods. We assumed a 15% rate of breastfeeding at 2 months corrected age according to French regional available data (unpublished data). We expected a relative improvement of 50% in the primary outcome i.e., an increase from 15% in the control group to 22.5% in the group with intervention. The coefficient of variation was set at 0.1 for a compromise between the recruitment capability of the sites and the required power. The type I error was fixed at 5% for a bilateral test. Under these hypotheses, the inclusion of 1 800 mother-child dyads (25 dyads per cluster and per time period) will allow to reach an approximate power of 80 %. To account for loss to follow-up and refusal of the intervention, we have added another 15% providing a sample of 2 080 mother-child dyads (28 dyads per cluster and per time period). Knowing that when possible,

all mother-infant pairs will be included in the case of a multiple birth and assuming a 15% rate of plural births, an average total of 2 400 mother-child dyads should be enrolled.

Analysis

- General analysis principles

Data analysis will be performed by an independent biostatistician at the Pôle de Santé Publique, Hospices Civils de Lyon, France. A full statistical analysis plan will be finalized prior to database lock. Statistical analysis and results will be reported according to the CONSORT guidelines for stepped wedge cluster randomized controlled trial.[41-42]

The analysis will be performed on the principle of intention-to-treat. The individual centres will be the unit of randomization and the individual mother-child dyads will be the unit of analysis.[43] All statistical tests and confidence intervals will be two-sided with a type I error set at alpha=0.05. Data monitoring will be done to insure the quality of the data collected by the centers in the eCRF. The analysis will be performed at the end of the follow-up using SAS statistical software (version 9.4, Inc).

- Descriptive analysis

Descriptive statistics will be calculated and compared to baseline characteristics of mother-child dyads enrolled during the control periods and the intervention periods using chi-square tests for categorical variables and Student's t tests for quantitative variables. Descriptive statistics will be performed at individual and cluster level using aggregate summary data.

- Analysis of the primary outcomes

To compare the breastfeeding rate at 2 months of corrected age, we will use generalized linear mixed models with a random effect for cluster, a fixed effect indicating the group assignment of each cluster at each step and a fixed effect of time (each period) to account for potential

secular changes during the study period.[40,44,45] The underlying form of time will be included in the model as a linear term or polynomial term, as appropriate. Further models will be fitted to test the heterogeneity of intervention across centres (including an interaction between intervention and centre as a fixed effect) and to test the heterogeneity of intervention across time periods (including an interaction between intervention and periods as a fixed effect). Analysis will be also adjusted for cluster-level covariates and for individual-level covariates unbalanced at baseline or known to be associated with breastfeeding status, such as mother's ethnicity, smoking status, mother's education level, breastfeeding history, caesarean delivery, birth term, or multiple birth. Results will be expressed as odds ratio and 95% CIs.

The breastfeeding rate at 2 months corrected age will be likely to be censored because of death and loss of follow-up. If so, the impact of intervention will be assessed using a Cox proportional hazard regression models. The estimated intervention effect will be reported as hazard ratio with 95% CIs.

- Implementation

Descriptive statistical analysis will be performed on peer counsellors data (number of peer counsellors recruited per centre, sociodemographic characteristics), on process variables to depict the intervention implementation in each centre (number of contacts received by dyad from peer counsellor, duration of contacts received, number of mothers who refused the intervention, number of mothers who interrupted the intervention and reason) and on satisfaction data

- Analysis of the secondary outcomes

Analysis of the secondary outcomes will proceed in the same way as for the primary outcome. Logistic regressions will be used for binary measurements, linear regression models for

continuous measurements and Cox proportional hazard regression models for survival analysis. The secondary outcomes will be exploratory.

- Medico-economic evaluation

For both medico-economics endpoints, costs will be evaluated in a societal perspective.. The French healthcare tariffs will be used to cost out resources consumed during the follow-up period.

To the specific cost of the intervention, the formation time, the indemnity for counsellors and the extra costs due to an increased time of the referent nurses or lactation consultant will be included. Each component will be costed out with a unit production cost or purchasing prices.

The ICER will be defined by the difference in cost between the two interventions, divided by the difference in effect express as the number of infants without impairment in each group.

The health outcomes of the cost-consequence analysis will be presented separately. Moreover, a budget impact analysis will be performed.

- Sensitivity analysis

Breastfeeding outcomes will be reanalysed in several post hoc sensitivity and restricted analyses. First, we will perform the analysis in the subgroup of mother-child dyads with a minimum 6-week duration of intervention. Second, the Swiss mother-child dyads will be excluded from the analysis, as a light version of peer counsellor support is already proposed in Switzerland.

The ICER will be calculated and sensitivity analysis (deterministic and probabilistic) will be performed to address uncertainty in cost and outcomes across both groups.

- Missing data

There will be no imputation of missing data; missing values will be left as missing for all statistical analyses (complete case analysis). Every effort will be made to minimize missing data including during follow-up.

Adverse events

Unexpected serious adverse events will be reported within 48 hours to the primary investigator of the study and to the members of the Data Safety and Monitoring Board in Switzerland. In France, due to the low risks, the adverse event declaration will follow the standard procedure of each hospital.

Data management

All study data will be entered by research staff in an electronic CRF. All data will be pre-coded and stored in a secured database.

Monitoring

Monitoring will be performed by a qualified person independent of the study group. Monitoring will check the notification of participation in the study and of no-opposition of the parents in medical chart in a sample of 20 charts in each centre. Specific consent will also be checked for participants in the sub-group of the economic study. At each visit, a CRF will be checked for eligibility criteria and the main outcome measure. If any deviation is noted, a next visit of monitoring will be performed.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent will be obtained by investigators from all individual participants involved in the study, this consent is oral in France and written in Switzerland and Belgium. A specific written consent is obtained for the medico economics ancillary study. The protocol has obtained the ethics approval from the "Comité de Protection des Personnes Sud-Est VI" with the ID-RCB: 2017-AO1977-46 in France. Local ethic committees have approved the study in Belgium(Comité d'Ethique du CHVE) and in Switzerland (*Commission cantonale d'éthique de la recherche sur l'être humain).* Important protocol modifications will be communicated to relevant parties following the relevant procedures.

All stored data are anonymized and protected by a password. The identification data is stored independently in another computer with another password.

The sponsor has an insurance to cover any harm from trial participation.

The study team will be committed to full disclosure of the results of the trial. The results of the study will be disseminated at several national and international academic and clinical meetings, and as articles published in national and international peer-reviewed journals. The study will be implemented and reported in-line with the CONSORT statement. Each paper or abstract will be submitted to the appropriate sub-committee for review of its appropriateness and scientific merit prior to submission. The study team will adhere to defined authorship criteria as per the International Committee of Medical Journal Editors. We used the SPIRIT reporting guidelines for this publication.[46]

Patient and Public Involvement

The design of the study was submitted to the « Réseau d'information et de soutient à l'allaitement maternel » in which an association of breastfeeding mothers is implicated. Furthermore, our intervention is a public intervention with a peer counselling.

SIGNIFICANCE AND OUTLOOK

Although the mother's own milk is an important protector in preterm infants, breastfeeding remains more difficult, less frequent and shorter in this vulnerable population. There is thus a critical need of evidence-based strategies to enhance breastfeeding outcomes in the NICU and after discharge. This large multi-centre study provides one of the first opportunities to test the feasibility and efficacy of breastfeeding peer counselling support system in Western European countries. Similarly to what has been shown for term infants in different settings, breastfeeding peer support could indeed constitute a feasible, acceptable, efficient, cost-effective, and thus sustainable intervention for preterm neonates. The provided emotional support could potentiate existing professional breastfeeding support.

We will evaluate the efficacy of the intervention on breastfeeding outcomes, neonatal mortality and morbidity, neurodevelopment and psychological health of the mother and mother-infant bounding as well as parenting stress. Due to the nature of the intervention, the communication with the mother is key, and sufficient French language skills are thus necessary. This will likely limit the inclusion of low income families. Psychological outcomes will solely be measured by self-report questionnaires, which is another limitation of the study. Finally, the medico-economical evaluation is based on infants from a specific French geographic region only. The results will therefore not be generalizable to the entire population. It was not feasible with our funding to study a larger population. However, if our study demonstrates that a peer counselling support is an efficacious and cost-efficient strategy to support and improve breastfeeding in NICUs, the intervention would likely be widely implemented.

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Author statement:

S Laborie chose the subject, wrote the initial draft; S Touzet proposed the design and supervised the redaction; P Occelli participate in the design and the redaction; J Margier designed and wrote the medico economics part; A Denis designed and wrote the statistical analysis; A Horsch designed and wrote the part on mental health; M Morisod Harari help A

Horsch on mental health's part,, O Claris supervised the work. C. J. Fischer Fumeaux contributed to plan the study. All the authors reviewed and revised the manuscript, and approved the final manuscript as submitted

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Data statement section

The trial statisticians will have access to the data set for the analysis of trial outcomes. The PI will have access to the data and will take full responsibility for the analysis and publication of the results. Once the main analyses have been undertaken, data will be available to principal and other investigators subject to approval of data analysis plans by the steering committee.

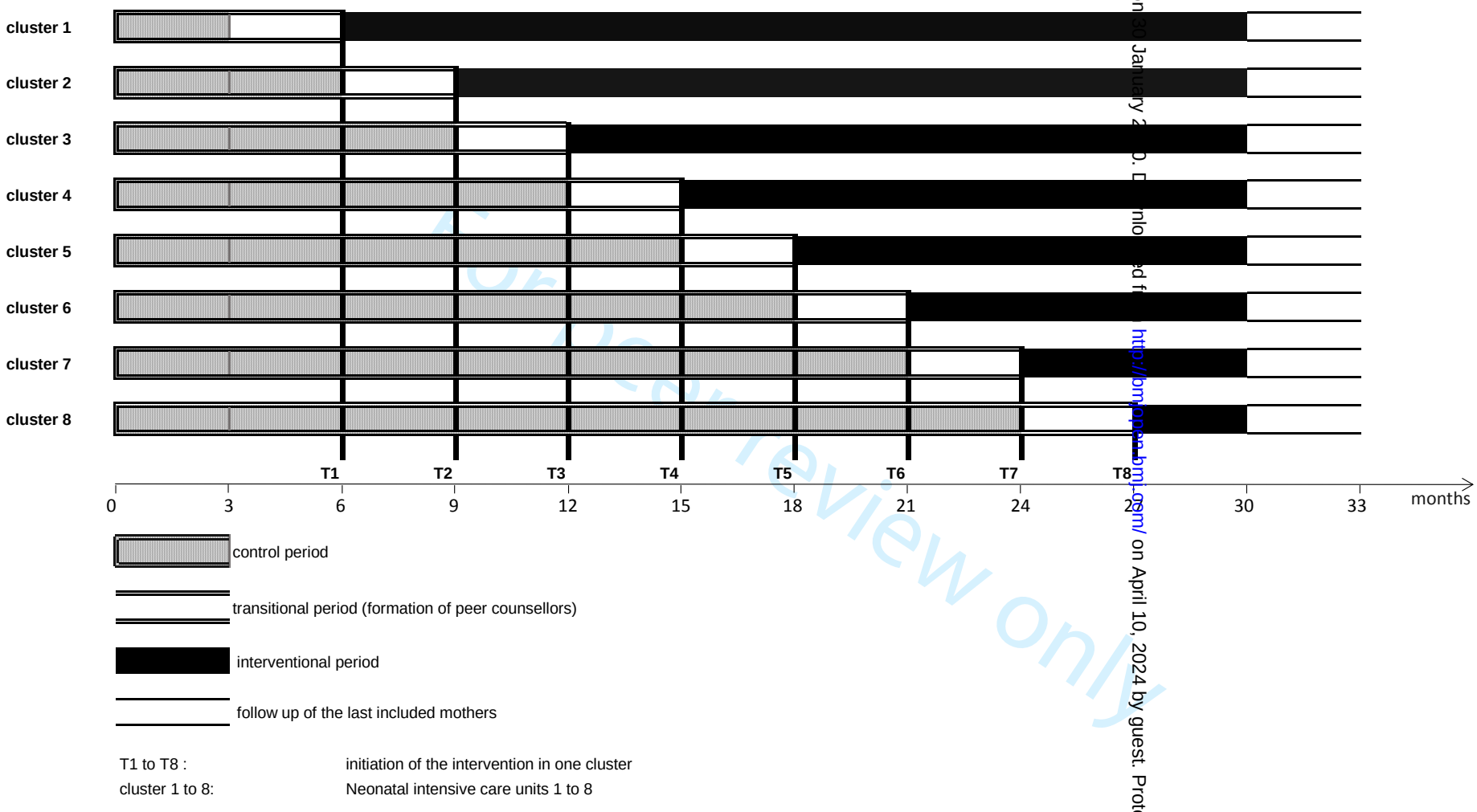
Disclaimer

The funders and sponsor have no role in study design, data collection, management, data analysis, and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication.

Conflicts of interests

None declared.

Figure 1 legend: Study design



CONSENTEMENT

La loi 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine rend obligatoire le recueil de l'accord écrit des parents des enfants sollicités pour participer à toute recherche interventionnelle ou recherche interventionnelle à risques et contraintes minimes. C'est un tel accord qui vous est demandé ci-dessous, pour que votre (vos) enfant(s) participe(nt) à l'étude intitulée :

Impact d'un accompagnement de l'allaitement de nouveau-nés prématurés par des mamans expérimentées : un essai randomisé en clusters multicentrique

Etude Eco-ALAÏS

Promoteur : Hospices Civils de Lyon

BP 2251

3 quai des Célestins,

69229 LYON cedex 02

Investigateur coordonnateur : Dr Sophie LABORIE

Service de réanimation néonatale et de néonatologie - HFME

Hospices Civils de Lyon

59 Boulevard Pinel

69677 Bron cedex

Tel: 04.27.85.56.99

sophie.laborie@chu-lyon.fr

Nous soussignés, …… …… *(NOMS, Prénoms)*, parents de …… …… *(NOM, Prénoms)* né(e)(s) le ……/……/……, *(JJ/MM/AAAA)* certifions avoir lu et compris la note d'information qui nous a été remise.

Nous avons eu la possibilité de poser toutes les questions que nous souhaitions au Pr/Dr/Mr/Mme …… *(NOM, Prénom)* qui nous a expliqué la nature, les c

Nous connaissons la possibilité qui nous est réservée d'interrompre la participation de notre ou nos enfant(s) à cette recherche à tout moment sans avoir à justifier notre décision et nous ferons notre possible pour en informer l'investigateur qui suit notre (nos) enfant(s) dans la recherche. Cela ne remettra naturellement pas en cause la qualité des soins ultérieurs.

Nous avons eu l'assurance que les décisions qui s'imposent pour la santé de notre enfant seront prises à tout moment, conformément à l'état actuel des connaissances médicales.

Nous avons bien compris que l'investigateur peut interrompre à tout moment la participation de notre enfant à l'essai s'il le juge nécessaire.

Nous sommes informés de la possibilité que les données de notre (nos) enfant(s) recueillies dans le cadre de cette étude puissent être réutilisées lors de recherches ultérieures exclusivement à des fins scientifiques et que nous pouvons nous y opposer.

Nous avons bien noté / été informés que cette recherche a reçu l'avis favorable du Comité de Protection des Personnes Sud Est VI le 01/09/2017et a fait l'objet d'une demande d'autorisation à la Commission Nationale Informatique et Libertés (CNIL).

Nous avons bien noté que cette recherche est menée conformément aux articles L1121-1 et suivants du Code de la Santé Publique, relatifs à la protection des personnes qui se prêtent à des recherches impliquant la personne humaine et conformément à la règlementation en vigueur.

Le promoteur de la recherche, les Hospices civils de Lyon, BP 2251, quai des célestins, 69229 Lyon cedex 02 a souscrit une assurance de responsabilité civile en cas de préjudice auprès de de la Société Hospitalière d'Assurance Mutuelle, 18 rue Edouard Rochet, 69008 Lyon, sous le numéro 153.930.

Nous acceptons que les personnes qui collaborent à cette recherche ou qui sont mandatées par le promoteur, ainsi qu'éventuellement le représentant des Autorités de Santé, aient accès à l'information contenue dans le dossier médical de notre (nos) enfant(s) dans le respect le plus strict de la confidentialité.

Nous acceptons que les données enregistrées à l'occasion de cette recherche puissent faire l'objet d'un traitement informatisé sous la responsabilité du promoteur.

Nous avons bien noté que, conformément aux dispositions de la loi relative à l'informatique, aux fichiers et aux libertés, nous disposons d'un droit d'accès, de rectification, de vérification, de correction et d'opposition à la transmission de nos données et celles de notre (nos) enfant(s). Nous disposons également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès de l'investigateur qui suit notre (nos) enfant(s) dans le cadre de cette recherche et qui connaît notre identité.

Notre consentement ne décharge en rien l'investigateur et le promoteur de la recherche de leurs responsabilités à l'égard de notre (nos) enfant(s). Nous et notre (nos) enfant(s) conservons tous les droits garantis par la loi.

Les résultats globaux de la recherche nous seront communiqués directement, si nous en faisons la demande, conformément à la loi du 4 mars 2002 relative aux droits des malades et à la qualité du système de santé.

Nous pouvons à tout moment demander des informations complémentaires au Dr Sophie Laborie (Tel : 04.27.85.56.99, sophie.laborie@chu-lyon.fr).

Trois exemplaires originaux de ce formulaire de consentement ont été établis : un nous a été remis, l'autre a été remis à l'investigateur et sera conservé au minimum 25 ans après la fin de la recherche. Le troisième exemplaire est destiné à l'assurance maladie.

- **PARENTS DONNANT LEUR CONSENTEMENT :**

A. AYANT DISPOSE D'UN TEMPS DE REFLEXION SUFFISANT AVANT DE PRENDRE NOTRE DECISION, NOUS ACCEPTONS LIBREMENT ET VOLONTAIREMENT **QUE NOTRE (NOS) ENFANT(S) ……**

B. **……**
……*(NOMS, PRENOMS)* PARTICIPE(NT) A L'ETUDE « ECO-ALAÏS ».

NOM, Prénom du 1er titulaire de l'autorité parentale : …….. Fait à …….. Le : |__|__|/|__|__|/|__|__|__|__| Signature :	NOM, Prénom du 2nd titulaire de l'autorité parentale : …….. Fait à …….. Le : |__|__|/|__|__|/|__|__|__|__| Signature :

C.

➢ **INVESTIGATEUR OBTENANT LE CONSENTEMENT :**

D. J'ATTESTE QUE TOUTES LES OBLIGATIONS LIEES A UN CONSENTEMENT ECLAIRE ONT ETE SATISFAITES DANS LE CADRE DE CE PROJET DE RECHERCHE CLINIQUE – QUE LES PARENTS DU (DES) PARTICIPANT(S) ONT REÇU UNE INFORMATION RELATIVE A LEUR DROITS, QUE NOUS AVONS DISCUTE DE CE PROJET ET QUE JE LEUR AI EXPLIQUE EN TERMES COMPREHENSIBLES L'ENSEMBLE DES INFORMATIONS CONTENUES DANS LA NOTICE. JE CERTIFIE EGALEMENT AVOIR LAISSE LES PARENTS DU (DES) PARTICIPANT(S) ME POSER TOUTES LES QUESTIONS QU'ILS SOUHAITAIENT ET Y AVOIR REPONDU.

NOM, Prénom de l'investigateur : ……

Fait à : ……, le |___|___| / |___|___| / |___|___|___|___|

Signature de l'investigateur :

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	29
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	28-29
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2

Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	29
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	29
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7,8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9,10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10,11
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or	11

		improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-16
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16,17
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a (centres' randomization)
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16

Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-16
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17,18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
Data monitoring:	#21b	Description of any interim analyses and stopping guidelines, including who will	n:a (no interim

interim analysis		have access to these interim results and make the final decision to terminate the trial	analyse)
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	29
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	29
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	21

authorship			
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	30-32
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

Notes:

- 16b: n/a (centres' randomization)
- 21b: n:a (no interim analyse) The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 11. July 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Breastfeeding peer counselling for mothers of preterm neonates: protocol of a stepped- wedge cluster randomized controlled trial.

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Breastfeeding peer counselling for mothers of preterm neonates: protocol of a stepped-wedge cluster randomized controlled trial.

Sophie Laborie[a], Angélique Denis[b], Antje Horsch[c,d], Pauline Occelli[b], Jennifer Margier[e], Mathilde Morisod Harari[f], Olivier Claris[a,g], Sandrine Touzet[b,h], Céline Julie Fischer Fumeaux[c].

Affiliations: [a]Hospices Civils de Lyon, Service de Réanimation Néonatale et Néonatologie, Hôpital Femme Mère Enfant, Bron, France; [b]Hospices Civils de Lyon, Pôle Santé Publique, Service recherche et épidémiologie clinique, Lyon, France; [c]Lausanne University Hospital, Clinic of Neonatology, Department Woman-mother-child, Lausanne, Switzerland; [d]Institute of Higher Education and Research in Healthcare, University of Lausanne, Lausanne, Switzerland; [e]Hospices Civils de Lyon, Pôle Santé publique, Service Evaluation Economique en Santé, Lyon, France; [f]Lausanne University Hospital, Service of Child and Adolescent Psychiatry, Lausanne, Switzerland; [g]Université Claude Bernard, Equipe P2S4129, Lyon, France ;[h] Université Claude Bernard Lyon 1, HESPER EA 7425, Lyon, France

Acronym : Alaïs

Correspondence to: Sophie Laborie, Service de Néonatologie et Réanimation Néonatale, Hospices Civils de Lyon - Hôpital Femme Mère Enfants, 59, Boulevard Pinel - 69677 Bron, France, [sophie.laborie@chu-lyon.fr], tel. +33 (0)4 27 85 52 84, fax +33 (0)4 27 86 92 27

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ABSTRACT

Introduction Among preterm infants, mother's own milk feeding reduces neonatal morbidity and decreases the length of hospital stay. However, breastfeeding rates and duration are lower than among term infants. It is reported that peer counselling is effective in increasing breastfeeding in term infants in low and middle income countries, but results are mixed in high income countries.

We aim to investigate herein whether peer counselling may be a feasible and effective breastfeeding support among preterm infants in French-speaking high income countries.

Methods and analysis Eight European centres will participate in this stepped-wedge cluster randomised controlled trial. We plan to include 2400 hospitalised neonates born before 35 gestational weeks. Each centre will begin with an observational period. Every three months, a randomized cluster (centre) will begin the interventional period with peer counsellors until the end of the study. The counsellors will be trained and supervised by trained nurses. They will have a weekly contact with participating mothers, with a face-to-face meeting at least once every fortnight. During these meetings, peer counsellors will listen to mothers' concerns, share experiences, and help the mother with their own knowledge of breastfeeding.

The main outcome is breastfeeding rate at 2 months corrected age. Secondary outcomes are breastfeeding rates at hospital discharge and at 6 months, breastfeeding duration and severe neonatal morbidity and mortality. The mental health of the mother, mother-infant bonding, and infant behaviour will be assessed using self-report questionnaires. A neuro-developmental follow-up, a cost-effectiveness analysis, and a cost-consequence at 2 years corrected age will be performed among infants in a French subgroup.

Ethics and dissemination French, Belgian and Swiss ethics committees gave their agreement. Publications in peer-reviewed journals are planned on breastfeeding, mental health and economic outcomes.

Trial registration number: NCT03156946

ARTICLE SUMMARY

Strengths and limitations of this study

- This study is the first multi-centre and multi-national randomised trial investigating the efficacy of peer counsellors to support and improve breastfeeding of preterm infants.
- This study gives us the opportunity to test the feasibility of such an intervention in Europe.
- The potential effect of peer counselling on maternal mental health and mother-infant bonding will also be investigated.
- The cost consequence analysis and the cost-effectiveness ratio expressed as the cost by avoided impairment at 2 years corrected age will be calculated for a subgroup of infants from a French geographic region.
- The measurement of psychological outcomes is limited by the use of self-report questionnaires.

INTRODUCTION

According to a recent meta-analysis, increasing breastfeeding rates following the World Health Organization recommendations could prevent yearly more than 800 000 deaths of children below the age of 5 years [1] and could save more than 300 billion dollars per year.[2]

Prematurity represents the leading cause of infant mortality around the world, and can lead to severe short- and long-term complications. In preterm neonates, mother's own milk feeding is associated with a significant decrease of severe morbidities, such as sepsis,[3-6] enterocolitis,[3,6,7] retinopathy of prematurity,[8] and bronchopulmonary dysplasia.[9] It has been shown to reduce the duration of hospital stay, as well as the risk of rehospitalisation.[10,11] In the same population, it is also associated with an increase of neuro-developmental or cognitive scores in infancy and childhood[12-15] with a dose-dependent effect.[12,16] However, studies have shown that breastfeeding rates of preterm infants at hospital discharge are far below those of term infants.[17]

In term infants, peer counselling by mothers with a previous positive experience of breastfeeding is effective in promoting breastfeeding in low and middle income countries (Relative risk 0.70, 95%Confidence nterval (CI)(0.60-0.82)).[18-21] In high income countries results are mixed.[18,21,22]

In neonatal intensive care units (NICUs), support by "veteran" parents with previous comparable experiences supporting NICU parents can have important benefits in term of psychological health for the parents, such as reduced stress, anxiety and depression, and increased perceived social support.[23] The studies on breastfeeding peer support in NICUs are scarce. An American randomized trial showed a significant increase in breastfeeding at 12 weeks postpartum in the group with peer counsellors (n=85, Odds Ratio 2,81 95% CI (1,1-7,14)).[24] Furthermore, the beneficial effect of peer support in NICUs increased even further

by the co-intervention of a breastfeeding consultant,[25] as already demonstrated for full-term infants.[26]

This multi-centre randomised cluster trial aims to study the effect of breastfeeding peer counselling for mothers of preterm neonates. The primary objective is to assess breastfeeding rates among preterm neonates at 2 months corrected age. The secondary objectives are to assess breastfeeding rates at hospital discharge and at 6 months, breastfeeding duration, and neonatal mortality and severe morbidity. Furthermore, psychological consequences of the intervention on maternal mental health, mother-infant bonding, and infant behaviour will be investigated. Moreover, we aim to assess satisfaction with the peer breastfeeding support and to measure its implementation. A neuro-developmental follow-up and a cost-effectiveness analysis at 2 years corrected age will be performed. Finally, the feasibility of such a peer support system for preterm breastfeeding support in European countries will be assessed.

METHODS

Design and setting

The study is a stepped wedge cluster randomised controlled trial. The design is presented in Figure 1. Each NICU corresponds to a cluster. All clusters start in the control situation at the beginning of the study. At each time step (every third month), a new cluster will cross over from the control period to the transition period and 3 months later to the intervention period. This design was chosen to prevent contamination of the intervention in the centre and to allow the delivery of the intervention in all participating centres.

The order of implementation is randomised, based on a computer-generated random sequence performed by an independent researcher. Due to the nature of the intervention it is not possible to blind mothers and teams in NICUs.

During the transition period, the centres do not contribute to analyses. This transition period takes into account the time it takes for the recruitment and training of peer counsellors (Figure 1).

The trial is conducted in eight NICUs, six of which are in France, one is in Switzerland and one in Belgium. One of the French centres is located in the Overseas Territories. The inclusions have started on 5 November 2018.

In each centre, two specialist lactation nurses or lactation consultants will supervise the peer support intervention. All supervisors participate in an identical 5-day training course, enabling them to recruit, train and supervise counsellors. This training is provided twice (in October 2018 for the first 4 centres and in November 2019 for the others) by an organisation (Association Relai Parentalité Allaitement) that has experience in training supervisors for peer support networks, including NICU networks.

Inclusion and exclusion criteria:

The mother and child dyads can be included if:

- Mothers:
    - Deliver before 35 weeks of gestational age
    - Do not present a medical contraindication to breastfeeding
    - Have sufficient language (French) skills to adequately participate in the study
    - Give their informed consent duringthe 7 days following delivery
- Neonates:

- Are admitted to a neonatal unit in the first 24 hours following birth
- do not present a medical contraindication to breastfeeding

Serious mental disorder in mothers and life threatening congenital malformations in infants constitute exclusion criteria.

Peer counsellors

Peers counsellors are eligible if they have breastfed at least one preterm infant hospitalized in a NICU, if they had a positive experience of breastfeeding, and if the breastfed child is in good health. In each NICU, all mothers of living former preterm babies aged between 1 and 3 years are invited to an information meeting. Thereafter the volunteers are interviewed and selected by the supervisors and participate in a 20-hour training programme led by the supervisors. The aim of the training is to provide them with knowledge about frequent difficulties encountered in breastfeeding of a preterm infant and to train them through role-plays to engage in a helping relationship.[27] They are not paid, although they will be partially compensated for travel or telephone costs. The number of peers selected depends on the size of each centre and varies from 9 to 29, taking into account an attrition rate of 30% per year. If needed, a new selection and training can be organised during the study.

Control period

The mothers will receive the professional breastfeeding support available (usual care). The organisation of this support depends on NICUs with various combinations and levels of support by nurses and/or breastfeeding consultants. In the Swiss centre, a collective peer support with a weekly meeting was already in place before the study: it will continue throughout the study.

After discharge, the mothers are supported by paediatric nurses and, in Switzerland and in Belgium, by independent midwifes.

The difference between usual care will be partly recorded in the case report form (CRF) (intent of breastfeeding, sources of information on breastfeeding during pregnancy, interval between birth and first use of breast pump or manual expression of milk, type of breastfeeding support received, number of skin-to-skin contacts during the first week, raw maternal milk administration and the date of first administration, date of first oral feeding and its modality, and duration of stay in a kangaroo/mother unit). It will also be evaluated for each centre through a questionnaire,[28] given to each unit at the initiation of the study, during the transition period and at the end of the study.

Intervention period

In addition to existing professional lactation support, mothers will receive an individual peer support by one of the peer counsellors.

Peer counsellors will first visit mothers either in the obstetrical unit before birth in case of premature delivery risk, or in the NICU. Then, during the NICU stay, at least weekly contact between peer counsellors and participating mothers (face-to-face, videotelephonyor telephone) will be planned, with a face-to-face meeting at least once every fortnight.

After infant discharge from the NICU, or if the infant is transferred to another hospital, the weekly contact will continue by phone until 1 month after the infant's return to the parental home. The minimum total number of contacts is five. The duration of the meetings is on average between three-quarter to 1 hour.

During these meetings, peer counsellors (matched for having had a child of comparable weight) will listen to mothers' concerns, share experiences on prematurity or breastfeeding, and help the mother with their own knowledge of breastfeeding. If they encounter difficulties, they can contact the supervisors individually or discuss them during a monthly supervisory group meeting. They record their interventions (dates, type, and topics).

The peer breastfeeding support is planned to stop in case of weaning or one month after hospital discharge, whichever occurs first. If the mother or the counsellor asks for discontinuation, another counsellor will be proposed to participating mothers.

Premature discontinuation of the intervention may happen in case of infant or maternal death, of withdrawal of consent, or if the mother asks for it and refuses another counsellor. In such cases, infants will be followed up until the end of the study period, except if the parents refuse this.

Outcomes and measures

- Primary outcome and measure

The primary outcome is breastfeeding rate at 2 months corrected age. An infant who received the mother's own milk during the preceding 48 hours will be considered as breastfed. The infant feeding will be assessed through telephone calls.

- Secondary outcomes and measures

  All measures and their timings are listed in Table 1.

Table 1: Measures and timing

	15 days of life	30 days of life	discharge	2 months corrected age	6 months corrected age	24 months corrected age
Breastfeeding (exclusive and mixed)			x	x	x	
Neonatal mortality and severe morbidity			x			
Neurodevelopment and sequelae						x
Psychological assessment	x	x			x	
Satisfaction of				x		

parents						
Economic costs	x	x	x	x	x	x

Breastfeeding

Breastfeeding initiation is defined as receiving at least once the mother's own milk. Breastfeeding at discharge is defined as receiving some mother's own milk during the 48 hours before NICU discharge. Breastfeeding at 6 months corrected age is defined as receiving any mother's own milk in the 48 hours before 6 months corrected age. Exclusive breastfeeding is defined as receiving neither other milk nor food than their mother's own milk during the 48 hours before discharge, and 2 and 6 months corrected age. Duration of breastfeeding is defined as duration from birth until last administration of mother's own milk. If breastfeeding is continuing at 6 months corrected age, the longer duration will not be recorded (censored data).

Neonatal mortality and severe morbidities

Mortality and the following complications (intra ventricular haemorrhage (grade > 2),[29] periventricular leukomalacia, enterocolitis stage > 1,[30] bronchopulmonary dysplasia defined as a persistent oxygen dependency or respiratory support at 36 weeks corrected age,[31] persistent ductus arteriosus requiring treatment, retinopathy of prematurity grade > 2,[32] sepsis (proven or probable)[33]) will be assessed during hospitalisation until 36 weeks corrected age.

Neurodevelopmental outcomes

In infants born before 33 weeks gestational age or with a weight below 1500g living in a specific geographic French area, the neurodevelopment will be assessed at 24 months using the Brunet Lezine scale.[34] The Brunet-Lezine scale measures 4 different subscores (gross motor function, fine motor function and visuospatial coordination, language, and sociability)

in children aged 2 to 30 months and calculates an overall neurodevelopmental score with a mean of 100, and a standard deviation of 15. The number of infants with cerebral palsy, deafness, blindness, developmental delay (neurodevelopmental score below 85) will be recorded in the same population during a paediatric consultation at 24 months corrected age.

Psychological outcomes:

- *Mothers*

Various mental health symptoms of the mothers will be assessed using several validated self-report questionnaires. The questionnaires will be completed by mothers reading French fluently.

i. Depressive symptoms in the last 7 days will be measured 15 days after birth and at 6 months corrected age using the Edinburgh Postnatal Depression Scale (EPDS),[35] which has been validated for pregnant women[36] and in a French sample, with good psychometric properties.[37]

ii. Anxiety symptoms will be assessed 15 days after birth and at 6 months corrected age using the Hospital Anxiety and Depression Scale (HADS), validated in French, with good psychometric properties.[38-40] The anxiety subscale has 7 items measuring state-anxiety in the last 7 days. It may be used as a measure of symptom severity.

iii. Mother-infant bonding will be measured using the Mother-Infant-Bonding Scale (MIBS),[41,42] 15 days after birth and at 6 months corrected age. In this questionnaire, the mother rates eight adjectives describing her feelings toward her infant that are indicative of mother-infant bonding.[41,42] This questionnaire was translated into French.[43]

iv. Maternal posttraumatic stress disorder symptoms will be assessed 1 month after childbirth and at 6 months corrected age using the Posttraumatic Checklist for DSM 5 (PCL-5).[44,45] This questionnaire has 20 items, measuring the 20 DSM-5 symptoms of

posttraumatic stress disorder (PTSD). It was translated into French and can also be scored to provide a provisional PTSD diagnosis.

v. Parenting stress will be evaluated at 6 months corrected age using the French version of the Parenting Stress Index Fourth Edition Short Form (PSI-4 SF),[46] which has 36 items assessing parental distress, dysfunctional parent-child interactions, and child difficulties. The PSI has good psychometric properties.[47]

Satisfaction of the mothers regarding the breastfeeding support and the intervention will also be assessed with a questionnaire designed for the study.

- *Infant behaviours*

Infant behaviour will be measured at 6 months corrected age using the French version of the Infant Behaviour Questionnaire – Revised (IBQ-R) Very Short Form.[48] The mother reports on a 7-points Likert scale the frequency of her infant's behaviours during the previous two weeks.[48]

- *Peer counsellors*

Depressive symptoms will be measured with the EPDS.[35,37] The satisfaction of peer counsellors will be measured using a questionnaire designed for the study.

- *Partners*

The partner's satisfaction on the intervention will be evaluated with a questionnaire designed for the study.

Economic outcomes

Cost data during the first two years will be gathered from a sub-population of infants included by centres in the Rhone-Alps region. To assess the total cost of each group, the amount of resources consumed (e.g., consultations, hospitalization, drugs, medical devices) will be extracted from the regional healthcare database and completed by the parents with their additional expenses (not covered by "the nationial social security system").

The primary economic endpoint will be the incremental cost-effectiveness ratio (ICER) at 2 years corrected age for intervention group versus control group. It will be expressed as incremental cost per impairment avoided. This outcome will be measured in the same subgroup as the neurodevelopmental outcome..

The secondary economic endpoint will be the cost-consequence analysis at 2 years corrected age. The health outcomes considered will be the mortality and the hospitalisation rates.

Feasibility of the intervention

The implementation of the intervention will be reported: number and characteristics of counsellors (age, place of birth, study level, parity, age of the previous preterm child), number of face-to-face meetings and of videotelephony or telephone contacts, duration and subjects treated in the meetings.

The number of mothers declining peer support counselling will be collected with the reason for refusal. The duration of counselling and the proportion of mothers ending the peer counselling prematurely and their reasons will also be collected.

Healthcare satisfaction

The satisfaction and the acceptability of the intervention by healthcare professionals (physicians and nurses) will also be evaluated by specific questionnaires developed for the study.

Blinding

Owing to the nature of the intervention, healthcare providers, parents and researchers will not be blind during the intervention phase.

Other changes occurring in the NICU during the study period

All events, such as organizational modifications that occur during the study period and may interact with the intervention or the study results will be recorded in a logbook.

Study sample size

We calculated the sample size for the stepped-wedge trial using the method reported by Hussey and Hughes.[49] The breastfeeding rate at 2 months corrected age was 15% according to French regional data (Réseau Ecl'aur, 2017). We expected a relative improvement of 50% in the primary outcome i.e., an increase from 15% in the control group to 22.5% in the group with intervention. The coefficient of variation was set at 0.1 for a compromise between the recruitment capability of the sites and the required power. The type I error was fixed at 5% for a bilateral test. Under these hypotheses, the inclusion of 1 800 mother-child dyads will allow to reach an approximate power of 80 %. To account for loss to follow-up and refusal of the intervention, we have added another 15% providing a sample of 2 080 mother-child dyads. Knowing that when possible, all mother-infant pairs will be included in the case of a multiple birth and assuming a 15% rate of plural births, a total of 2 400 mother-child dyads should be enrolled.

Analysis

- General analysis principles

A full statistical analysis plan will be finalised prior to database lock. Statistical analysis and results will be reported according to the CONSORT guidelines for stepped wedge cluster randomised controlled trial.[50-51]

The analysis will be performed according to the intention-to-treat principle. The individual centres will be the unit of randomisation and the individual mother-child dyads will be the

unit of analysis.[52] All statistical tests and confidence intervals will be two-sided with a type I error set at alpha=0.05.

- Descriptive analysis

Descriptive statistics will be calculated and compared to baseline characteristics of mother-child dyads enrolled during the control periods and the intervention periods using the Chi-squared test for categorical variables and the Student's t tests for quantitative variables.[53] Descriptive statistics will be provided at the individual and cluster level using aggregate summary data.

- Analysis of the primary outcomes

To compare the breastfeeding rate at 2 months corrected age, we will use generalised linear mixed models with a random effect for cluster, a fixed effect indicating the group assignment of each cluster at each step, and a fixed effect of time (each period) to account for potential secular changes during the study period.[49,54,55] The underlying form of time will be included in the model as a linear term or polynomial term, as appropriate. Further models will be fitted to test the heterogeneity of intervention across centres (including an interaction between intervention and centre as a fixed effect) and to test the heterogeneity of intervention across time periods (including an interaction between intervention and periods as a fixed effect). Analyses will also be adjusted for cluster-level covariates and for individual-level covariates unbalanced at baseline or known to be associated with breastfeeding status, such as mother's ethnicity, smoking status, mother's education level, breastfeeding history, caesarean delivery, gestational age, multiple birth, and recorded differences in usual cares. Duration of peer support will also be controlled for. Results will be expressed as odds ratio and 95% CIs.

The breastfeeding rate at 2 months corrected age will be likely to be censored because of death and loss of follow-up. If so, the impact of intervention will be assessed using a Cox

proportional hazard regression models. The estimated intervention effect will be reported as hazard ratio with 95% CIs.

- Implementation

Descriptive statistical analysis will be performed on data relating to peer counsellors (number of peer counsellors recruited per centre, sociodemographic characteristics), on process variables to describe the intervention implementation in each centre (number of contacts received by dyad from peer counsellor, duration of contacts received, number of mothers who refused the intervention, number of mothers who interrupted the intervention and reason) and, on data related to satisfaction.

- Analysis of the secondary outcomes

Analysis of the secondary outcomes will be conducted in the same way as for the primary outcome. Logistic regressions will be used for binary measurements, linear regression models for continuous measurements and Cox proportional hazard regression models for survival analysis. The secondary outcomes will be exploratory.

- Economic evaluation

For both economic endpoints, costs will be evaluated from a societal perspective. The French healthcare tariffs will be used to cost out resources consumed during the follow-up period.

The specific cost of the intervention (training time, indemnity for counsellors, and extra costs due to an increased working time of the referent nurses or lactation consultants) will be included. Each component will be costed out using a unit production cost or a purchasing price.

The ICER will be defined by the difference in cost between the two interventions, divided by the difference in outcome expressed as the number of infants without impairment in each group.

The health outcomes of the cost-consequence analysis will be presented separately. Moreover, a budget impact analysis will be performed.

- Sensitivity analysis

Breastfeeding outcomes will be reanalysed in several post hoc sensitivity and restricted analyses. First, we will perform the analysis in the subgroup of mother-child dyads with a minimum intervention duration of 6 weeks. Secondly, the Swiss mother-child dyads will be excluded from the analysis, as a light version of peer counsellor support is already proposed in Switzerland.

The ICER will be calculated and sensitivity analysis (deterministic and probabilistic) will be performed to address uncertainty in cost and outcomes across both groups.

- Missing data

There will be no imputation of missing data. Every effort will be made to minimise missing data including during follow-up.

Adverse events

Unexpected serious adverse events will be reported within 48 hours to the primary investigator of the study and to the members of the Data Safety and Monitoring Board in Switzerland. In France, due to the low risks, the adverse event declaration will follow the standard procedure of each hospital.

Data management

All study data will be entered by research staff in an electronic CRF. All data will be pre-coded and stored in a secured database.

Monitoring

Monitoring will be performed by a qualified person independent of the study group. Monitoring will check the notification of participation in the study and of no-opposition of the parents in a sample of 20 participants in each centre. Specific consent will also be checked for participants in the sub-group used for the economic study. At each visit, a CRF will be checked for eligibility criteria and the main outcome measure. If any deviation is noted, an additional monitoring visit will be performed.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the 1964 Helsinki Declaration and its later amendments. Informed consent will be obtained by investigators from all individual participants involved in the study, this consent is oral in France and written in Switzerland and Belgium. A specific written consent is obtained for the ancillary economic study. The protocol has obtained the ethics approval from the "Comité de Protection des Personnes Sud-Est VI" with the ID-RCB: 2017-AO1977-46 in France. Local ethic committees have approved the study in Belgium (Comité d'Ethique du CHVE) and in Switzerland (Commission cantonale d'éthique de la recherche sur l'être humain). Important protocol modifications will be communicated to relevant parties following the relevant procedures.

All stored data are anonymised and protected by a password. The identification data is stored independently in another computer with another password.

The sponsor has an insurance to cover any harm from trial participation.

The study team will be committed to full disclosure of the results of the trial. The results of the study will be disseminated at several national and international academic and clinical meetings, and as articles published in national and international peer-reviewed journals. The study will be implemented and reported in-line with the CONSORT statement. Each paper or abstract will be submitted to the appropriate sub-committee for review of its appropriateness and scientific merit prior to submission. The study team will adhere to defined authorship criteria as per the International Committee of Medical Journal Editors. We used the SPIRIT reporting guidelines for the present publication.[56]

Patient and Public Involvement

The design of the study was submitted to the "Réseau d'information et de soutien à l'allaitement maternel " in which an association of breastfeeding mothers is implicated. Furthermore, our intervention is carried out by peers (experts by experience).

SIGNIFICANCE AND OUTLOOK

Although the mother's own milk is an important protector in preterm infants, breastfeeding remains more difficult, less frequent and shorter in this vulnerable population. There is thus a critical need of evidence-based strategies to enhance breastfeeding outcomes in the NICU and after discharge. This large multi-centre study provides one of the first opportunities to test the feasibility and efficacy of breastfeeding peer counselling support system in Western European countries. Similarly to what has been shown for term infants in different settings, breastfeeding peer support could indeed constitute a feasible, acceptable, effective, efficient, and thus sustainable intervention for preterm neonates. The provided emotional support could potentiate existing professional breastfeeding support.

We will evaluate the efficacy of the intervention on breastfeeding outcomes, neonatal mortality, severe morbidities, neurodevelopment and psychological health of the mother and mother-infant bounding, as well as parenting stress. Due to the nature of the intervention, the communication with the mother is key, and sufficient French language skills are thus necessary. This will likely limit the inclusion of low-income families. Psychological outcomes will solely be measured by self-report questionnaires, which is another limitation of the study. It would have been interesting to include a qualitative process evaluation component. Finally, the economic evaluation is based on infants from a specific French geographic region only. The results will therefore not be generalisable to the entire population. It was not feasible with the funding obtained to study a larger population. However, if the study demonstrates that a peer counselling support is an effective and cost-efficient strategy to support and improve breastfeeding in NICUs, the intervention is likely to be widely implemented.

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Author statement:

S Laborie chose the subject, wrote the initial draft; S Touzet proposed the design; P Occelli participated in the design and the redaction; J Margier designed the medico economic part; A Denis designed the statistical analysis; A Horsch and M Morisod Harari designed the part on

mental health; O Claris and C. J. Fischer Fumeaux contributed to plan the study. All the authors reviewed and revised the manuscript, and approved the final manuscript as submitted

Conflicts of interests

None declared.

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Data sharing statement: Data from our clinical trial will be available upon reasonable request

Disclaimer

The funders and sponsor have no role in study design, data collection, management, data analysis, and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication.

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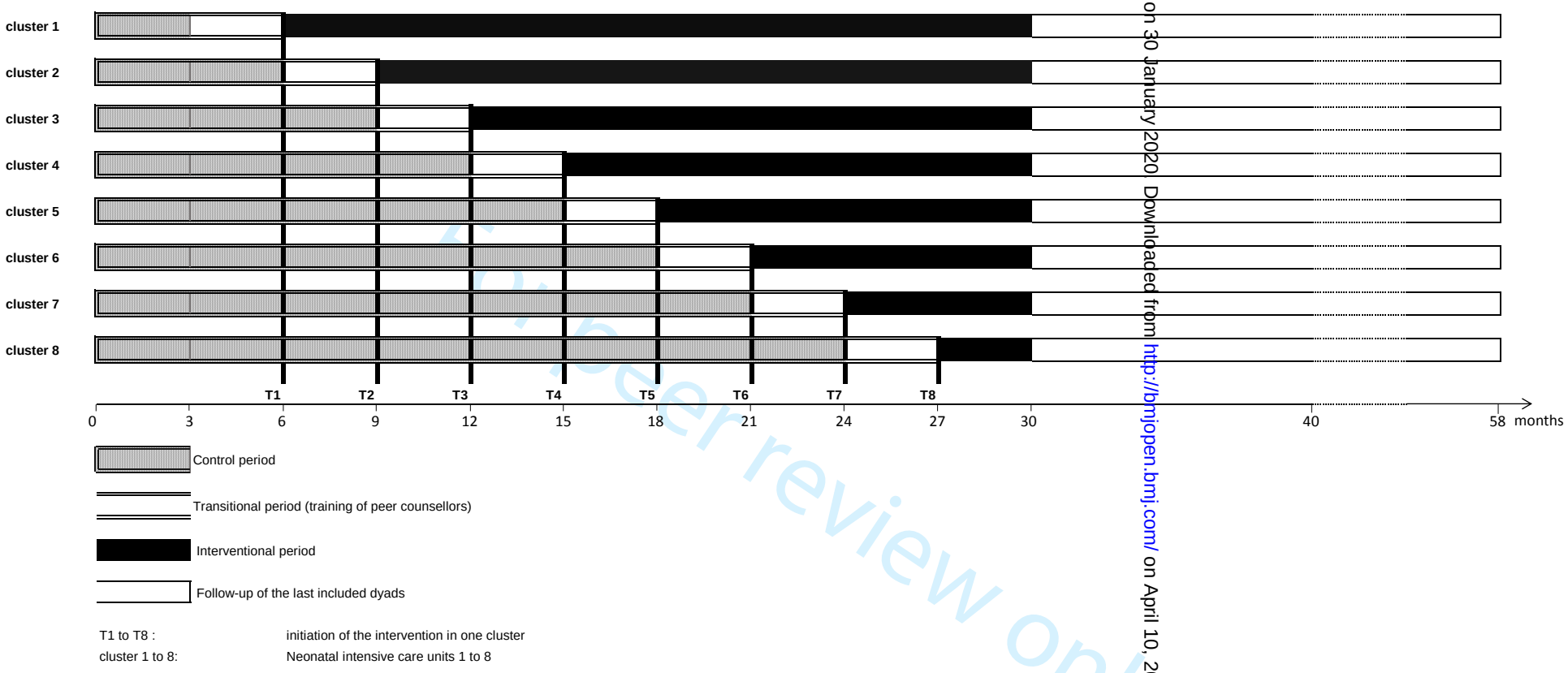
Legend:. Figure 1 : Study design



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1,28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,28
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	29
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18,29

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-13, Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___14_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____6_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____6_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____5,6_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___13,14_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___9-13_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____9_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	29
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21,29
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	28
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	apppendices
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.