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JOINT OBSERVATION IN NICU (JOIN): CLINICAL RANDOMIZED CONTROLLED TRIAL EXAMINING AN EARLY INTERVENTION DURING PRETERM CARE

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KEYWORDS

Early intervention, preterm, neonate, developmental care, self-efficacy, parenting, infant development, mother

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ABSTRACT

Introduction

Preterm birth may generate significant distress among the parents, who often present with difficulties in appropriating their parental role and low parental self-efficacy. Parental stress and low parental self-efficacy may in turn interfere with the infant's socioemotional and cognitive development especially through disrupted parent-infant interactions. Perceived parental self-efficacy represents the belief of competence in caring for one's own infant and successful incarnation of the parental role, as well as the skills required for parenting. Interventions to support parental competences in parents of very preterm infants, as well as infant development, are needed.

Methods and analysis

This study protocol describes a randomized controlled trial that will test an early intervention in the NICU (JOIN: Joint Observation In Neonatology) carried out by an interdisciplinary staff team. Mothers of preterm neonates born between 28 and 32 6/7 weeks of gestational age are eligible for the study. The intervention consists of a videotaped observation by a clinical child psychologist or psychiatrist and a study nurse of a period of care delivered to the neonate by the mother and a NICU nurse. The care procedure is followed by an interactive video guidance intended to reinforce parental competences and perceived self-efficacy, and to demonstrate the neonate's abilities and resources to his parents.

The primary outcome will be the difference in the perceived maternal self-efficacy between the intervention and control groups assessed by self-reported questionnaires.

Secondary outcomes will be the maternal mental health, the perception of the parent-infant relationship, the maternal responsiveness, and the neurodevelopment of the infant at 6 months corrected age.

Ethics and dissemination

Ethical approval was granted by the Human Research Ethics Committee of the Canton de Vaud (study number 496/12). Results from the study will be disseminated at national and international conferences, and in peer-reviewed journals.

Trial registration number

clinicaltrials.gov (NCT02726136)

ABBREVIATIONS

BSID-III: Bayley Scales of Infant Development, 3rd Edition / CA: corrected age / CRIB: Clinical Risk Index for Babies / EAS: Emotional Availability Scales / EPDS: Edinburgh Postnatal Depression Scale / F-PSS NICU: Parental Stressor Scale Neonatal Intensive Care Unit / GA: Gestational Age / HADS: Hospital Anxiety and Depression Scale / IBQ-R: Infant Behavior Questionnaire-Revised / MIBS: Mother-to-Infant Bonding Scale / mMOS-SS: Modified Medical Outcomes Study Social Support Survey / NICU: Neonatal Intensive Care Unit / PDS-F: Posttraumatic Diagnosis Scale / PMP-SE: Perceived Maternal Self-Efficacy / PSI: Parental Stress Index / PTSD: Post-Traumatic Stress Disorder

ARTICLE SUMMARY

Strengths and limitations of this study

- The study will test the effects of an early intervention carried out by an interdisciplinary partnership between NICU nurses and clinical child psychologists/ psychiatrists.
- Among other objectives, the intervention aims at increasing perceived parenting self-efficacy in mothers of very preterm infants.
- The intervention draws on theories of neonatal and infant development, as well as interactive video guidance.
- Methodological rigour, including concealment of random allocation and prospective trial registration and publication, limits risk of bias.
- Unblinded participants and clinicians may increase the risk of bias.

INTRODUCTION

Advances in Neonatal Care

Improvement of pre- and postnatal care over the past decades has led to increased survival of very preterm neonates born less than 32 weeks' gestation [1]. Among others, protective measures to promote health and subsequent neurodevelopment have been developed, including optimization of nutritional support, better characterization of neonatal stress, and improved pain management. In the same perspective, developmental care was introduced in the Neonatal Intensive Care Units (NICU) since the 90's with the intention of minimizing the adverse consequences of prematurity on the developing brain. During a critical period of development, the preterm brain is highly vulnerable to injury, represented by cerebral haemorrhage and insult to the white matter. Additionally, beyond the injury, preterm neonates are prone to alteration of brain maturation with disruption of normal developmental trajectory of both grey and white matters [2-4].

Developmental Care

Over the last two decades, a growing body of research focused on the impact of excessive stimuli such as sound, light, touch or pain on the preterm neonate, hypothesizing that an unfavourable and stressful environment may add to the adverse effects of neonatal morbidity [5]. These concerns led progressively to the introduction of developmental care, which consists of individualized strategies mainly based on the neonate's skills and/or difficulties [6], and supporting the neonate's regulation and development. The first aim of the developmental care is to limit exposure to deleterious environmental stimulations. Management of sensorial dystimulation, as well as of pain and stress during invasive care

procedures, represents a central target of developmental care [7 8]. The second main objective focuses on the child's well-being through the adaptation of the sensorial environment in order to provide more physiological external stimuli (tactile, auditory, visual, vestibular), that will help to promote behaviours and postures fostering comfort and regulation. The third objective of the developmental care aims to support parents in their role and to strengthen the relationship they are developing with their child [7 9]. Although studies have found contradictory results [10-12], some evidence shows a positive impact of developmental care on short- and long-term neonatal and neurodevelopmental outcomes [13-16].

Impact of prematurity on parents' well-being

Preterm birth and caring for a preterm infant may be distressing for parents, who often feel vulnerable and incompetent in the high-tech NICU environment [17-19]. Parents may present with difficulties in understanding and capturing subtle cues from their infant [20]. Parents show important signs of stress [21], and require more support during the first year after the preterm birth compared with parents of term infants [22]. They may also experience mental health symptoms, including posttraumatic stress disorder (PTSD) [23-29], anxiety, and depression [19 30].

Although the hospitalization of a preterm neonate may affect both parents equally [30], most of the studies examining parental emotional distress focused on mothers' experience and needs [18 31 32]. After birth, the mother normally initiates specific behaviours towards her newborn, which aim at supporting the neonate who experiences high levels of stress during hospitalization in the NICU [33], and foster the infant's socioemotional development [34 35]. However, mothers of preterm infants may present difficulties in

developing these protective behaviours [36]. Thus, parental stress may interfere with the infant's socioemotional and cognitive development, and is associated with more difficulties in building positive parent-infant relationships due to disrupted interactions [34 37 38]. However, a recent meta-analysis showed that mothers of preterm children were not less sensitive or responsive toward their children than mothers of full-term children [39].

Parenting self-efficacy

Parenting self-efficacy is defined as 'beliefs or judgements a parent holds of their capabilities to organize and execute a set of tasks related to parenting a child'[40]. Self-efficacy includes two separate notions; first, the belief of competence in caring for one's own child and successful incarnation of the parental role (general self-efficacy) [41], and secondly, the skills required for parenting (specific self-efficacy) [42]. The present study will focus on the specific self-efficacy, which drives actions and predicts parents' performances and behaviours [43 44].

As demonstrated in previous studies, parenting self-efficacy appears to mediate the relationship between psychosocial risk factors and maternal competences [45 46]. Thus, a perception of low self-efficacy is associated with parental depression [45 47-50], high levels of parenting stress [51 52], low family support [53], poor infant health [52 54], and demanding infant temperament [55 56]. In contrast, a perception of high self-efficacy is associated with sensitive and receptive parental behaviour, and is related to improved infant socioemotional development [49 57].

Parents of preterm neonates face a complex challenge. While they might be responsive to their infant cues, preterm neonates might not be capable of engaging in sustained and responsive interaction, as they tend to be less attentive and reactive due to

immaturity, and to show more negative behaviours and emotions, as well as less rewarding interactions than their term-born peers [49 58-60]. In parallel, mothers of preterm neonates, who are at risk of experiencing depression, anxiety or post-traumatic disorder [19 29], may not be able to interact as adequately with their child, and could be less sensitive than mothers without mental health symptoms. Mothers of preterm infants may be at a higher risk of decreased maternal confidence [61], although the limited evidence available so far is mixed [50 62]. The quality of care provided by parents is strongly influenced by the maternal perception of self-efficacy, and interventions promoting this may therefore help to increase parenting quality [63 64].

To date, only few early interventions have focused on enhancing perceived parenting self-efficacy. The interventions that are currently available in the early neonatal period mainly aim to decrease parental trauma and stress-related symptoms, and to improve parental responsiveness within the parent-infant interaction [17 65-67]. Thus, a recent meta-analysis identified only two interventions intended to increase maternal self-efficacy [68-70]. These two interventions concentrated on different techniques of parenting education, and one of the two demonstrated improved cognitive child development at 4 months of age [70]. The present study focuses on the joint observation, which is an interdisciplinary intervention performed in the NICU soon after birth with distinct objectives. Among them, increasing perceived parenting self-efficacy may represent a good indicator of the effects of this early intervention.

Joint observation

The joint observation (JOIN: Joint Observation In Neonatology [71]) was developed in line with the three objectives of the developmental care model. This early intervention

program in the NICU is carried out by an interdisciplinary partnership between NICU nurses or paediatricians and clinical psychologists or child psychiatrists.

This intervention is based on four distinct theories describing neonatal and infant development. First, the evaluation of neonatal behaviour developed by Brazelton and Nugent [72] underlines the importance of parents detecting the neonate's competences and fragilities, and interpreting stress cues to adjust to the infant's regulation needs. Second, the synactive model of Als [73] proposes a program of individualized care avoiding overstimulation in the NICU and supporting the neonate's self-regulation and competences. Third, the sensorimotor approach elaborated by Bullinger [74] consists mainly of the assessment of sensory dystimulations provided to the neonate, and the management of subsequent tonico-postural disturbances observed during the NICU stay with the long-term perspective of optimizing his development. This approach builds a framework to adjust the care procedures to the neonate's capacity to treat multisensory information, and to reach a sensoritonic balance that allows and supports interactive behaviours. Fourth, the interactive guidance is a model based on the observation and analysis of parent-infant interactions trough the therapeutic use of video-feedback [75-77]. This approach aims to allow parents to become aware of their competences and resources, as well as the skills and needs of their infant. Video-feedback has recently been studied as an intervention in the NICU [78 79]. The authors postulated that the interactive guidance through video-feedback reduces the negative impact of preterm birth on the parent-infant relationship, and the behavioural withdrawal of the parent. Results revealed increased parental sensitivity and positive effects on the developing relationship [78]. A longitudinal study implementing video-feedback not only during the NICU stay, but also during the first year of life specifically demonstrated

effects on parental stress, interactive behaviours, as well as on neuroendocrine regulation in children [80].

The joint observation pragmatically consists of two phases. Firstly, a video-recorded period of routine care for the preterm neonate (such as a nappy change) is carried out by both the parent (mostly the mother) and a NICU nurse. Secondly, several short extracts of the period of care are carefully selected by the observers in order to reach the main objective of the intervention that can be summarized as follows: increasing the parents' confidence in caring for their own infant, as well as in their own capacity to build the parent-infant relationship, and to support their infant's development. With this main goal in mind, observers will play back the extracts to the parents, showing short specific moments of interactive behaviours that usually escape awareness. This video-feedback is conducted in order to point out the quality of the relational and emotional parent-infant interactions, and highlights moments of attunement, adjustment, synchrony, reciprocity and mutuality.

Three additional objectives of the joint observation can be added to the main objective: 1) The neonate's adaptive capacity and competences are highlighted, as well as his interactive signals, in order to promote parents' emotional involvement, awareness of the infant's perspective, resources and needs. 2) To reinforce parental responsiveness, the parent's behaviours that are supporting the neonate's signals are pointed out during the video extracts, highlighting the parental relational competences frequently unidentified by the parents themselves. 3) With the aim of developing individualized care, measures can be suggested acknowledging the specificities of each neonate (sensorial irritability, tonico-postural disturbances or withdrawal for instance), and adjusting the care to reinforce the neonate's own capacity of auto-regulation and to support his sensoritonic balance development in a long-term perspective.

Aims of the present study

The objectives of the present study are to measure the effects of the joint observation as an early intervention performed in the NICU on outcomes relative to parental perception and mental health, as well as to indices of the parent-infant relationship quality and of child development. The primary outcome measure will be the perceived maternal self-efficacy. Secondary objectives will be to measure the impact of this intervention on maternal mental health (including perceived stress, posttraumatic stress, anxiety, depression), on maternal perception of the parent-infant relationship, on maternal responsiveness, and on the neurodevelopment of the infant at 6 months corrected age (CA). In addition, acceptability of the intervention and maternal satisfaction will be assessed.

METHODS AND ANALYSIS

Study Design

We will conduct a monocentric randomized controlled trial testing an intervention compared with treatment-as-usual, in the level III NICU of a Swiss University Hospital.

Study population, recruitment, group allocation, and blinding

All mothers of preterm neonates born between 28 and 32 6/7 weeks of gestational age (GA), admitted to the NICU, and aged less than 8 weeks of life are eligible to participate. Exclusion criteria include the following: maternal age <18 years, established intellectual disability or psychotic illness, insufficient French-speaking level to fulfil questionnaires, and cardio-respiratory instability of the preterm neonate (severe brady-apnea syndrome, oxygen requirement >30%). Regarding twins or triplets, only the first-born neonate or the one being more stable will be included in the study.

Recruitment will be performed by the study nurses, who approach the eligible mothers once their infants are stable enough. The allocation ratio of randomisation is 1:1, using a computer-generated list of random blocks (https://www.sealedenvelope.com/simple-randomiser). The allocation sequence will be concealed from the principal investigator in sequentially numbered, opaque, sealed envelopes. Envelopes will be opened only after the enrolled participants gave signed consent and completed all baseline assessments. The principal investigator and the statistician will be blind to group allocation. All participant data will be coded to ensure confidentiality.

Control group

Participants in the control group will receive treatment-as-usual. They will be asked to complete questionnaires at the same time-points as the participants in the intervention group: at recruitment, at one month after enrolment, and at 6 months of their infant's corrected age (CA). At 6 months CA, a neurodevelopmental assessment of the infant and a 10-min filmed mother-infant interaction will take place.

Intervention group

Mothers assigned to the intervention group will be asked to complete self-report questionnaires at the three time-points described above. The intervention in the form of the joint observation will be planned after enrolment depending on the infant's clinical state and stability. The intervention is two-fold: firstly, two professionals (a study nurse, a child psychologist or psychiatrist) are jointly observing a period of care administered to the neonate jointly by her mother and a NICU nurse. The care procedure is video-taped and an observation grid [81] is completed by the observer. Secondly, the mother and the NICU nurse participate in a video-feedback session with the two observers. The discussion is based on the principles of interactive guidance [78], as described above. At the end of the intervention, the mother will also be asked to complete a questionnaire regarding her satisfaction with the intervention.

At 6 months CA, a neurodevelopmental assessment of the infant and a 10-min filmed mother-infant interaction will be carried out.

Primary outcome

The primary outcome is the difference in perceived maternal self-efficacy between the control and intervention groups measured with the *Perceived Maternal Parenting Self-Efficacy* (PMP-SE) questionnaire one month after study enrolment.

Secondary outcomes

Maternal outcomes

Using validated self-reported questionnaires described below, various aspects of maternal well-being will be compared between the two groups at baseline and at the 1-month and 6-month follow-up, including symptoms of PTSD (*Posttraumatic Diagnosis Scale),* parental stress (*Parental Stressor Scale: Neonatal Intensive Care Unit* and *Parenting Stress Index-Short form)*, anxiety (*Hospital Anxiety and Depression Scale)* and depression *(Edinburgh Postnatal Depression Scale).* Other measures will include maternal perception of the parent-infant relationship *(Mother-to-Infant Bonding Scale)* and of her infant's temperament (*Infant Behaviour Questionnaire – Revised*), perceived social support (*Modified Medical Outcomes Study Social Support Survey)*, and maternal sensitivity or responsiveness (*Emotional Availability Scales* and *Care Index*). In addition, acceptability and maternal satisfaction of the intervention will be assessed in the intervention group.

Neonatal outcomes

The neurodevelopmental outcome of the preterm neonates will be measured at 6 months CA (*Bayley Scales of Infant Development, 3rd Edition [BSID-III]*).

Data collection and visits

After enrolment, mothers will be asked to complete several questionnaires described below, and again one month after study enrolment, and at 6 months CA. Infants will return at 6 months CA to the neonatal follow-up clinic for the neurodevelopmental assessment and the 15-min filmed mother-infant interaction. The study measures and timings are summarized in Table 1 and Figure 1.

Measures

Self-report questionnaires

Perceived Maternal Parenting Self-Efficacy (PMP-SE)

This questionnaire including 20 items, which represent 4 subscales (care taking procedures, evoking behaviour(s), reading behaviours or signalling, and situational beliefs), was specifically developed for mothers of preterm neonates, and has good psychometric properties [42]. Responses to each item are recorded on a four-point Likert scale (from 'strongly disagree' – score 1 to 'strongly agree' – score 4). To obtain a French version of the questionnaire, a translation and cultural adaptation was performed with the forward-backward method [82].

Posttraumatic Diagnosis Scale (PDS-F)

Maternal PTSD is measured using this 17-items scale based on DSM-IV criteria. Mothers will rate frequency and severity of symptoms, such as re-experiencing, avoidance and hyperarousal, experienced over the last month, and graded on a four-point Likert scale. The PDS displays good psychometric properties [83], and a French version has been validated [84].

Parental Stressor Scale: Neonatal Intensive Care Unit (F-PSS: NICU)

The questionnaire assessed parental stress with 31 items focusing on their perception of stress factors during the NICU stay of their neonate and explores three domains: impact of the visual and auditory environment, behaviour and aspect of the neonate, and parental role [85].

Parenting Stress Index-Short form (PSI-SF)

This 36-items questionnaire is a shortened version of the *Parental Stress Index* [86], which measures the stress related to parenthood, and is intended for parents of children 0 to 3 years. The three subscales investigate parental distress, dysfunctional interactions between the parents and the child, and child difficulties. Its validity has been demonstrated in studies of parents of preterm neonates [87]. In this study, the validated French version will be used [88].

Hospital Anxiety and Depression Scale (HADS)

Anxiety and depression symptoms are assessed using the French version of the HADS, which includes 14 items, and measures the severity of symptoms [89]. This questionnaire has good psychometric properties [90].

Edinburgh Postnatal Depression Scale (EPDS)

Maternal depression symptoms will also be assessed with the EPDS, which focuses on the symptoms experienced over the last 7 days [91]. The French version displays good psychometric characteristics [92].

Mother-to-Infant Bonding Scale (MIBS)

In this questionnaire, the mother rates (from 0 to 5) eight adjectives describing her feelings toward her infant, which is indicative of mother-infant bonding [93 94] and was translated into French [95].

Infant Behaviour Questionnaire – Revised (IBQ-R) Very Short Form

Infant temperament is assessed through the French version of this questionnaire (total of 191 items). The parent reports on a 7-points Likert scale the frequency of his infant's behaviours during the previous two weeks [96].

Modified Medical Outcomes Study Social Support Survey (mMOS-SS)

This validated self-reported evaluation consisting of eight items measuring different aspects of social support [97] is based on the 19-items questionnaire assessing the dimensionality of four functional support scales (emotional/informative, tangible, affectionate, and positive social interaction) [98]. A French translation and cultural adaptation was performed using the forward-back method [82].

Questionnaire of satisfaction and acceptability of the intervention

This questionnaire comprises a general question on maternal satisfaction with the intervention and six questions on its setting, value and usefulness, which will provide a qualitative evaluation. In addition, three questions focus on the acceptability of the intervention by the mothers.

Demographic and perinatal characteristics

Mothers will also report demographic information, including socio-economic status, level of education [99], and previous psychiatric disease. Neonatal characteristics will be collected from the medical record on severity of morbidity (GA and weight at birth, Apgar score, complications – need for mechanical ventilation and respiratory morbidity, sepsis, and cerebral lesions), as well as the Clinical Risk Index for Babies (CRIB) [100], which represents neonatal morbidity severity.

Assessment of maternal sensitivity and responsiveness

Maternal sensitivity will be assessed at 6 months CA by coding a session of free play between the mother and her infant with the *Emotional Availability Scales* (EAS) [101]. Six domains are evaluated, of which four relate to the mother's behaviour (sensitivity, structuration, intrusion and hostility toward the infant), and two to the infant's behaviour (reactivity to the mother and maternal involvement). Patterns of interaction and emotional availability can therefore be measured on separate scales [102].

A second tool, the *Care Index* [103], will measure maternal sensitivity, by assessing the interactive behaviour within the mother-infant dyad according to seven scales (facial expressions, vocalizations, posture, expressed affection, turn-taking, control and activity). Three maternal (sensitive, controlling, passive) and four infant (cooperative, compulsive-compliant, demanding, passive) characteristic behaviours are coded on each scale.

Neurodevelopmental assessment of the infant

A standardized neurodevelopmental assessment will be conducted at 6 months CA by a developmental paediatrician, using the Bayley Scales of Infant Development, 3rd Edition

[104], which entails three subscales (cognitive, language and motor) with a normative mean score of 100 ± 15 SD.

Sample size calculation

Power calculation (G*Power)[105] based on published means and standards deviations [42 48] related to perceived parental self-efficacy in a sample of preterm (*M* = 58.51, *SD* = 12.57) and of term-born (*M* = 65.9, *SD* = 8.2) neonates showed that 68 participants would need to be recruited (α = 0.05, 1-β = 0.80, unilateral hypothesis). This is based on the assumption that parental self-efficacy in mothers of preterm babies in the intervention group who benefitted from the intervention would be comparable to that in mothers of term babies. Therefore, it is planned that 80 mothers will be enrolled to anticipate possible participant withdrawal.

STATISTICAL ANALYSES

For the primary outcome regarding the difference in the perceived maternal self-efficacy between the intervention and control groups, linear regression analysis will be employed. For the secondary aims, the analyses will be performed both for differences in changes between the intervention and the control group and for differences between groups at different time points using linear regression analysis. Associations between outcomes will be tested using linear regression analyses.

Differences between groups will be adjusted for the respective baseline values in case they differ. Variables will be transformed if residuals are not normally distributed. We will include potential confounding variables, if necessary. These include maternal age, sex of

the children, and socioeconomic status where applicable. For confirmatory analyses, a Bonferroni correction for multiple analyses will be applied. For initial exploratory analyses, no such correction will be used [106].

ADVERSE EVENTS

Expected and unexpected adverse events will be recorded during the study period. As the intervention does not involve medical or pharmaceutical treatment, the risk that an adverse event would occur is low. A child psychiatrist will be available for clinical assessment and follow-up if needed, particularly if significant psychological distress or psychiatric illness is detected during study participation.

DATA MANAGEMENT

All study data will be coded and entered by research staff (psychology assistant). The database will be regularly updated by the IT Service of the Lausanne University Hospital. Double data entry will be done for the primary outcomes. For the rest of the data, a random 5% will be double-checked. The principal investigator, the co-investigators and the statistician will have access to the final trial dataset. Individual participant data collected during the trial (after deidentification) on which publications from JOIN consortium are based will be available on reasonable request.

ETHICS AND DISSEMINATION

The local ethical committee (Commission d'Ethique du Canton de Vaud, Switzerland, study number: 496/12) approved the study protocol. Little to no risk is expected by participation of the mothers and their neonates to the trial. Signed informed consent will be

obtained from all participating mothers. Participation in the study will not interfere with the typical care patients receive after childbirth and during NICU stay. Results from the study will be disseminated at national and international conferences, and in peer-reviewed journals. This randomized controlled trial is registered in *clinicaltrials.gov* (NCT02726136).

SIGNIFICANCE AND OUTLOOK

This study might result in an evidence-based early intervention aiming to reinforce parental competences, in particular to increase perceived parental self-efficacy. It would represent a brief, easily accessible, and safe early intervention, which could be implemented in the routine care in the NICU, thus leading to significant changes in clinical practice. It will also help to characterize the relationships between perceived parental self-efficacy, maternal mental health, maternal perception of their relationship with their infant and their infant's temperament, and maternal sensitivity.

Due to its interdisciplinary nature, this research is of interest for clinicians, educators and researchers in the field of paediatrics and development, psychology, psychiatry, and public health.

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COLLABORATORS

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AUTHOR CONTRIBUTIONS

NF and AH designed the study with input from all other members of the consortium. AB and MMH designed the intervention with input from members of the consortium. JS and AH drafted the manuscript and contributed equally to the present work. AB, MMH, NF, CT, AL and JFT significantly contributed to the establishment and refinement of study procedures and critically revised the manuscript. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

None declared.

ETHICAL APPROVAL

Ethical approval was granted by the Human Research Ethics Committee of the Canton de Vaud (study number 496/12).

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Table 1

Measures	Questionnaires	T1 Baseline	T2 One month post-intervention	T3 Follow-up at 6 months CA
Perceived maternal self-efficacy	PMP-SE	x	x	x
Maternal well-being	PDS-F	x	x	x
	F-PSS NICU	x	x	
	PSI	x	x	x
	HADS	x	x	x
	EPDS	x	x	x
Mother-infant relationship	MIBS	x	x	x
Maternal perception of her infant's temperament	IBQ-R	x	x	x
Maternal sensitivity				x
Maternal satisfaction	Satisfaction questionnaire		x	
Perceived social support	mMOS-SS	x	x	x
Perinatal risk severity	CRIB	x		
Neurodevelopmental assessment	BSID-III			x

Table 1 summarizes the measures at the 3 different time-points.

Abbreviations: CA: corrected age; PMP-SE: Perceived Maternal Self-Efficacy; PDS-F: Posttraumatic Diagnosis Scale; F-PSS NICU: Parental Stressor Scale Neonatal Intensive Care Unit; PSI: Parental Stress Index; HADS: Hospital Anxiety and Depression Scale; EPDS: Edinburgh Postnatal Depression Scale; MIBS: Mother-to-Infant Bonding Scale; IBQ-R: Infant Behavior Questionnaire-Revised; mMOS-SS: Modified Medical Outcomes Study Social Support Survey; CRIB: Clinical Risk Index for Babies; BSID-III: Bayley Scales of Infant Development, 3rd Edition

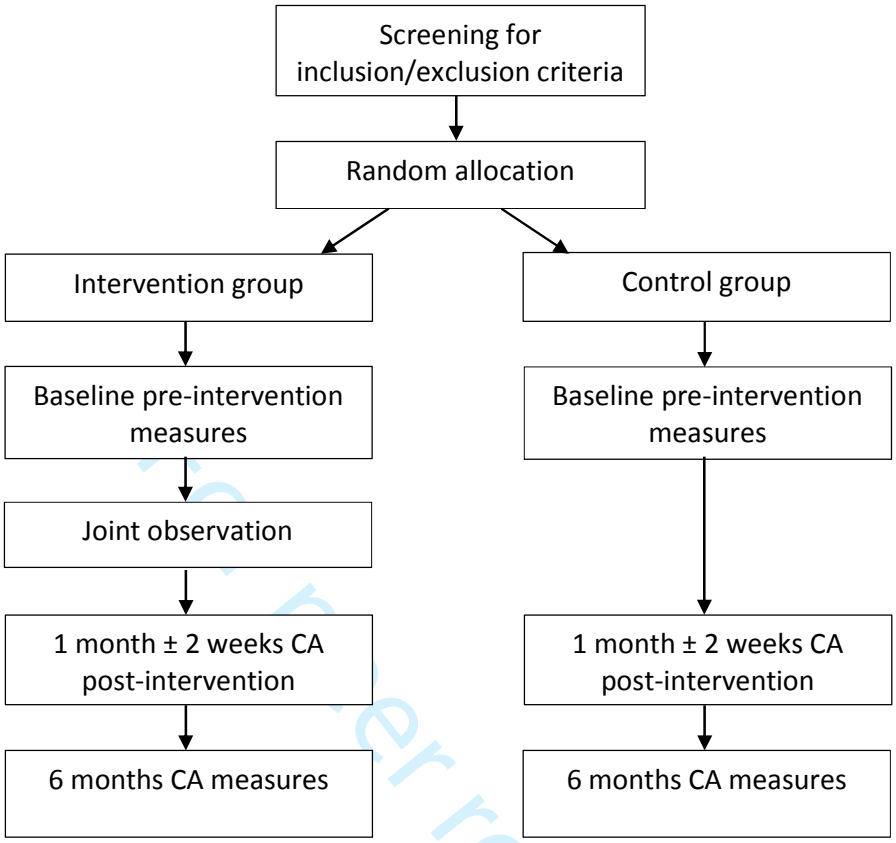

Figure 1: Flow-chart of the study. Abbreviations: CA: corrected age

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	4
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	n/a
	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	n/a
	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)	n/a

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	8-11
	6b	Explanation for choice of comparators	13-14
Objectives	7	Specific objectives or hypotheses	12
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)	13
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	13
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)	13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11, 14, Table 1, Figure 1
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
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	14-15
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)	15-16, Table 1, Figure 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	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
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	13
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	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	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 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	15-20
	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	n/a

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	21
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	20-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
	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)	21
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	n/a
	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	n/a
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21-22
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)	21-22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, 21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13, 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	13, 21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
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
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	n/a
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	21-22
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	upon request
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

*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.

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JOINT OBSERVATION IN NICU (JOIN): STUDY PROTOCOL OF A CLINICAL RANDOMIZED CONTROLLED TRIAL EXAMINING AN EARLY INTERVENTION DURING PRETERM CARE

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JOINT OBSERVATION IN NICU (JOIN): STUDY PROTOCOL OF A CLINICAL RANDOMIZED CONTROLLED TRIAL EXAMINING AN EARLY INTERVENTION DURING PRETERM CARE

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Early intervention, preterm, neonate, developmental care, self-efficacy, parenting, infant development, mother

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ABSTRACT

Introduction

Preterm birth may generate significant distress among the parents, who often present with difficulties in appropriating their parental role. Parental stress and low perceived parental self-efficacy may interfere with the infant's socioemotional and cognitive development, particularly through disrupted parent-infant interactions. Perceived parental self-efficacy represents the belief of efficacy in caring for one's own infant and successful incarnation of the parental role, as well as the perception of one's own abilities to complete a specified task. Interventions to support parental role, as well as infant development, are needed, and parental self-efficacy represents a useful indicator to measure the effects of such early interventions.

Methods and analysis

This study protocol describes a randomized controlled trial that will test an early intervention in the NICU (JOIN: Joint Observation In Neonatology) carried out by an interdisciplinary staff team. Mothers of preterm neonates born between 28 and

32 6/7 weeks of gestational age are eligible for the study. The intervention consists of a videotaped observation by a clinical child psychologist or child psychiatrist and a study nurse of a period of care delivered to the neonate by the mother and a NICU nurse. The care procedure is followed by an interactive video guidance intended to demonstrate the neonate's abilities and resources to his parents.

The primary outcome will be the difference in the perceived maternal self-efficacy between the intervention and control groups assessed by self-report questionnaires. Secondary outcomes will be maternal mental health, the perception of the parent-infant relationship, maternal responsiveness, and the neurodevelopment of the infant at 6 months corrected age.

Ethics and dissemination

Ethical approval was granted by the Human Research Ethics Committee of the Canton de Vaud (study number 496/12). Results from this study will be disseminated at national and international conferences, and in peer-reviewed journals.

Trial registration number

clinicaltrials.gov (NCT02736136)

ABBREVIATIONS

BSID-III: Bayley Scales of Infant Development, 3rd Edition / CA: corrected age / CRIB: Clinical Risk Index for Babies / EAS: Emotional Availability Scales / EPDS: Edinburgh Postnatal Depression Scale / F-PSS NICU: Parental Stressor Scale Neonatal Intensive Care Unit / GA: Gestational Age / HADS: Hospital Anxiety and Depression Scale / IBQ-R: Infant Behavior Questionnaire-Revised / MIBS: Mother-to-Infant Bonding Scale / mMOS-SS: Modified Medical Outcomes Study Social Support Survey / NICU: Neonatal Intensive Care Unit / PDS-F: Posttraumatic Diagnosis Scale / PMP-SE: Perceived Maternal Self-Efficacy / PSI: Parental Stress Index / PTSD: Post-Traumatic Stress Disorder

ARTICLE SUMMARY

Strengths and limitations of this study

- The study will test the effects of an early intervention carried out by an interdisciplinary partnership between NICU nurses and clinical child psychologists/ child psychiatrists.
- Among other objectives, the intervention aims at increasing perceived parental self-efficacy in mothers of very preterm infants.
- The intervention draws on theories of neonatal and infant development, as well as interactive video guidance.
- Methodological rigour, including concealment of random allocation and prospective trial registration and publication, limits risk of bias.
- Unblinded participants and clinicians may increase the risk of bias.

INTRODUCTION

Advances in Neonatal Care

Improvement of pre- and postnatal care over the past decades has led to increased survival of very preterm neonates born less than 32 weeks' gestation [1]. Among others, protective measures to promote health and subsequent neurodevelopment have been developed, including optimization of nutritional support, better characterization of neonatal stress, and improved pain management. In the same perspective, developmental care was introduced in the Neonatal Intensive Care Units (NICU) since the 90's with the intention of minimizing the adverse consequences of prematurity on the developing brain. During a critical period of development, the preterm brain is highly vulnerable to injury, represented by cerebral haemorrhage and insult to the white matter. Additionally, beyond the injury, preterm neonates are prone to alteration of brain maturation with disruption of normal developmental trajectory of both grey and white matters [2-4].

Developmental Care

Over the last two decades, a growing body of research focused on the impact of excessive stimuli such as sound, light, touch or pain on the preterm neonate, hypothesizing that an unfavourable and stressful environment may add to the adverse effects of neonatal morbidity [5]. These concerns led progressively to the introduction of developmental care, which consists of individualized strategies mainly based on the neonate's skills and/or difficulties [6], and supporting the neonate's regulation and development. The first aim of the developmental care is to limit exposure to deleterious environmental stimulations. Management of sensorial dystimulation, as well as of pain and stress during invasive care procedures, represents a central target of developmental care [7 8]. The second main objective focuses on the child's well-being through the adaptation of the sensorial environment in order to provide more physiological external stimuli (tactile, auditory, visual, vestibular), that will help to promote behaviors and postures fostering comfort and regulation. The third objective of the developmental care aims to support parents in their role and to strengthen the relationship they are developing with their child [7 9 10]. Although studies have found contradictory results [11-13], some evidence shows a

positive impact of developmental care on short- and long-term neonatal and neurodevelopmental outcomes [14-19].

Impact of prematurity on parents' well-being

Preterm birth and caring for a preterm infant may be distressing for parents, who often feel vulnerable and incompetent in the high-tech NICU environment [20-22]. Parents may present with difficulties in understanding and capturing subtle cues from their infant [23]. Parents show important signs of stress [24], and require more support during the first year after the preterm birth compared with parents of term infants [25]. They may also experience mental health symptoms, including posttraumatic stress disorder (PTSD) [26-32], anxiety, and depression [22 33].

Although the hospitalization of a preterm neonate may affect both parents equally [33], most of the studies examining parental emotional distress so far focused on mothers' experience and needs [21 34 35]. After birth, the mother normally initiates specific behaviors towards her newborn, aimed at supporting the neonate who experiences high levels of stress during hospitalization in the NICU [36], and at fostering the infant's socioemotional development [37 38]. However, mothers of preterm

infants may present difficulties in developing these protective behaviours [39]. Thus, parental stress may interfere with the infant's socioemotional and cognitive development, and is associated with more difficulties in building positive parent-infant relationships due to disrupted interactions [37 40 41]. However, a recent meta-analysis showed that mothers of preterm children were not less sensitive or responsive toward their children than mothers of full-term children [42].

Perceived parental self-efficacy

Perceived parental self-efficacy is defined as 'beliefs or judgements a parent holds of their capabilities to organize and execute a set of tasks related to parenting a child'[43]. Self-efficacy includes two separate notions; first, the belief of efficacy in caring for one's own child across several varied domains of functioning and successful incarnation of the parental role (general self-efficacy) [44-46] , and secondly, the perception of one's own abilities to complete a specified task within a specific domain (specific self-efficacy) [47]. The present study will focus on the specific self-efficacy, which appears to drive actions and predicts parents' behaviors [45 48].

As demonstrated in previous studies, perceived parental self-efficacy appears to mediate the relationship between psychosocial risk factors and maternal competences [49 50]. Thus, a perception of low self-efficacy is associated with parental depression [49 51-54], high levels of parenting stress [55 56], low family support [57], poor infant health [56 58], and demanding infant temperament [59 60]. In contrast, a perception of high self-efficacy is associated with sensitive and receptive parental behavior, and is related to improved infant socioemotional development [53 61].

Parents of preterm neonates face a complex challenge. While they might be responsive to their infant cues, preterm neonates might not be capable of engaging in sustained and responsive interaction, as they tend to be less attentive and reactive due to immaturity, and to show more negative behaviors and emotions, as well as less rewarding interactions than their term-born peers [53 62-64]. In parallel, mothers of preterm neonates, who are at risk of experiencing depression, anxiety or post-traumatic disorder [22 32], may not be able to interact as adequately with their child, and could be less sensitive than mothers without mental health symptoms. Mothers of preterm infants may be at a higher risk of decreased maternal confidence [65], although the limited evidence available so far is mixed [54 66]. The quality of care

provided by parents is strongly influenced by the maternal perception of self-efficacy, and interventions promoting this may therefore help to increase parenting quality [46 67].

To date, only few early interventions have focused on enhancing perceived parental self-efficacy. The interventions that are currently available in the early neonatal period mainly aim to decrease parental trauma and stress-related symptoms, and to improve parental responsiveness within the parent-infant interaction [10 20 68-70]. Thus, a recent meta-analysis identified only two interventions intended to increase perceived maternal self-efficacy [71-73]. These two interventions concentrated on different techniques of parenting education, and one of the two demonstrated improved cognitive child development at 4 months of age [73]. The present study focuses on the joint observation, which is an interdisciplinary intervention performed in the NICU soon after birth. The main aim of the study is to examine whether this early intervention increases perceived parental self-efficacy.

Joint observation

The joint observation (JOIN: Joint Observation In Neonatology [74]) was developed in line with the three objectives of the developmental care model. This early intervention program in the NICU is carried out by an interdisciplinary partnership of professionals, thereafter called observers, including NICU nurses, paediatricians, clinical child psychologists or child psychiatrists. They all received a 20 hours training, delivered by the same experienced clinical child psychologist (AB) for consistency, and participate in regular supervision sessions during the study period.

The intervention combines elements issued from four distinct theories of neonatal and infant development. First, the evaluation of neonatal behaviour developed by Brazelton and Nugent [75] underlines the importance of parents detecting the neonate's competences and fragilities, and interpreting stress cues to adjust to the infant's regulation needs. Second, the synactive model of AIs [76] proposes a program of individualized care avoiding overstimulation in the NICU and supporting the neonate's self-regulation and competences. Third, the sensorimotor approach elaborated by Bullinger [77] consists mainly of the assessment of sensory dystimulations provided to the neonate, and the management of subsequent tonico-

postural disturbances observed during the NICU stay with the long-term perspective of optimizing his development. This approach builds a framework to adjust the care procedures to the neonate's capacity to treat multisensory information, and to reach a sensoritonic balance that allows and supports interactive behaviours. Fourth, the interactive guidance is a model based on the observation and analysis of parent-infant interactions trough the therapeutic use of video-feedback [78-80]. This approach aims to allow parents to become aware of their competences and resources, as well as the skills and needs of their infant. Video-feedback has recently been studied as an intervention in the NICU [81 82]. The authors postulated that the interactive guidance through video-feedback reduces the negative impact of preterm birth on the parent-infant relationship, and the behavioural withdrawal of the parent. The results of this previous work have revealed increased parental sensitivity and positive effects on the developing relationship [81]. A randomized clinical study implementing video-feedback not only during the NICU stay, but also during the first year of life specifically demonstrated positive effects on parents of preterm infants with a lowering of mothers' post-traumatic stress symptoms and enhancement in maternal sensitivity and quality of mother-infant interactions[83].

In order to address the main objective, the present intervention is focusing on following areas: 1) The neonate's adaptive capacity and competences are highlighted, as well as his interactive signals, in order to promote parents' emotional involvement, awareness of the infant's perspective, resources, and needs. For instance, the neonate's interactive initiatives, as well as his responses to parental touch and/or voice, such as eye opening or head turning, will be highlighted. 2) To reinforce parental responsiveness, the parent's behaviors that are supporting the neonate's signals are pointed out during the video extracts, highlighting the parental relational competences frequently unidentified by the parents themselves. For example, positive emotional interactions between the mother and her neonate will be emphasized, such as adapting the voice and facial expression in order to support the neonate's alertness. 3) With the aim of developing individualized care, measures can be suggested acknowledging the specificities of each neonate (sensorial irritability, tonico-postural disturbances or withdrawal for instance), and adjusting the care to reinforce the neonate's own capacity of auto-regulation and to support his sensoritonic balance development in a long-term perspective. For instance, the parent's gestures of support according to the baby's tonico-postural needs will be

identified, such as supporting the baby's neck or pelvis while interacting with him or adjusting the rhythm to help the neonate developing auto-regulation competencies.

The joint observation pragmatically consists of two phases. Firstly, a video-recorded period of routine care for the preterm neonate (such as a nappy change) is carried out by both the parent (mostly the mother) and a NICU nurse for a duration of approximately 30 minutes.

There is no intervention by the observers during the videotaping. Secondly, before gathering with the mother, several short extracts of the period of care are carefully selected by the observers in order to reach the objectives of the intervention. During the discussion and for illustration purpose, the observers will play back 4-6 short extracts of 10-30 seconds each to the parents, showing short specific moments of interactive behaviors that usually escape awareness. This video-feedback, which lasts about 60 minutes, is conducted in order to point out the quality of the relational and emotional parent-infant interactions, and highlights moments of attunement, adjustment, synchrony, reciprocity, and mutuality.

Aims of the present study

The objectives of the present study are to measure the effects of the joint observation as an early intervention performed in the NICU on outcomes relative to parental perception and mental health, as well as to indices of the parent-infant relationship quality and of child development. The primary outcome measure will be the perceived maternal self-efficacy. Secondary objectives will be to measure the impact of this intervention on maternal mental health (including perceived stress, post-traumatic stress, anxiety, depression), on maternal perception of the parent-infant relationship, on maternal responsiveness, and on the neurodevelopment of the infant at 6 months corrected age (CA). In addition, acceptability of the intervention and maternal satisfaction will be assessed.

METHODS AND ANALYSIS

Study Design

We will conduct a monocentric randomized controlled trial testing an intervention compared with treatment-as-usual, in the level III NICU of a Swiss University Hospital.

Study population, recruitment, group allocation, and blinding

All mothers of preterm neonates born between 28 and 32 6/7 weeks of gestational age (GA), admitted to the NICU, and aged less than 8 weeks of life are eligible to participate. Exclusion criteria were set for ethical considerations and in order to avoid approaching mothers needing acute treatment, and include the following: maternal age <18 years; established intellectual disability or psychotic illness; insufficient French-speaking level to complete questionnaires due to impossibility to obtain valid translations to multiples languages for financial reasons; and cardio-respiratory instability of the preterm neonate (severe brady-apnea

syndrome, oxygen requirement >30%) to ensure his survival during the study period. Regarding twins or triplets, only the first-born neonate or the one being more stable will be included in the study.

Recruitment will be performed by the study nurses, who approach the eligible mothers once their infants are stable enough, i.e., after the critical period of the first week of life when cardio-respiratory stability is established, usually on non-invasive ventilation and with oxygen requirement <30%, which would also permit more active participation of the parents in the neonate's care. The allocation ratio of randomisation is 1:1, using a computer-generated list of random blocks (https://www.sealedenvelope.com/simple-randomiser). The allocation sequence will be concealed from the principal investigator in sequentially numbered, opaque, sealed envelopes. Envelopes will be opened only after the enrolled participants gave signed consent and completed all baseline assessments. The principal investigator and the statistician will be blind to group allocation. All participant data will be coded to ensure confidentiality.

Control group

Participants in the control group will receive treatment-as-usual. They will be asked to complete questionnaires at the same time-points as the participants in the intervention group: at recruitment, at one month after enrolment, and at 6 months of their infant's corrected age (CA). At 6 months CA, a neurodevelopmental assessment of the infant and a 10-min filmed mother-infant interaction will take place.

Intervention group

Mothers assigned to the intervention group will be asked to complete self-report questionnaires at the three time-points described above. The intervention in the form of the joint observation will be planned after enrolment depending on the infant's clinical state and stability. The intervention is two-fold: firstly, the observers are jointly observing a period of care administered to the neonate jointly by her mother and a NICU nurse. The care procedure is video-taped and an observation grid [84] is completed by the observers. Secondly, the mother and the NICU nurse participate in a video-feedback session with the two observers. The discussion is based on the principles of interactive guidance [81], as described above. At the end of

the intervention, the mother will also be asked to complete a questionnaire regarding her satisfaction with the intervention.

At 6 months CA, a neurodevelopmental assessment of the infant and a 10-min filmed mother-infant interaction will be carried out.

Primary outcome

The primary outcome is the difference in perceived maternal self-efficacy between the control and intervention groups measured with the *Perceived Maternal Parenting Self-Efficacy* (PMP-SE) questionnaire one month after study enrolment.

Secondary outcomes

Maternal outcomes

Using validated self-reported questionnaires described below, various aspects of maternal well-being will be compared between the two groups at baseline and at the 1-month and 6-month follow-up, including symptoms of PTSD (*Posttraumatic Diagnostic Scale),* parental stress (*Parental Stressor Scale: Neonatal Intensive Care Unit* and *Parenting Stress Index-Short form)*,

anxiety (*Hospital Anxiety and Depression Scale)* and depression *(Edinburgh Postnatal Depression Scale).* Other measures will include maternal perception of the parent-infant relationship *(Mother-to-Infant Bonding Scale)* and of her infant's temperament (*Infant Behaviour Questionnaire – Revised*), perceived social support (*Modified Medical Outcomes Study Social Support Survey)*, and maternal sensitivity or responsiveness (*Emotional Availability Scales* and *Care Index*). In addition, acceptability and maternal satisfaction of the intervention will be assessed in the intervention group.

Neonatal outcomes

The neurodevelopmental outcome of the preterm neonates will be measured at 6 months CA (*Bayley Scales of Infant Development, 3rd Edition [BSID-III]*).

Data collection and visits

After enrolment, mothers will be asked to complete several questionnaires described below, and again one month after study enrolment, and at 6 months CA.

Infants will return at 6 months CA to the neonatal follow-up clinic for the neurodevelopmental assessment and the 10-min filmed mother-infant interaction. The study measures and timings are summarized in Table 1 and Figure 1.

Measures

Self-report questionnaires

Perceived Maternal Parenting Self-Efficacy (PMP-SE)

This questionnaire including 20 items, which represent 4 subscales (care taking procedures, evoking behaviour(s), reading behaviours or signalling, and situational beliefs), was specifically developed for mothers of preterm neonates, and has good psychometric properties [47]. Responses to each item are recorded on a four-point Likert scale (from 'strongly disagree' – score 1 to 'strongly agree' – score 4). To obtain a French version of the questionnaire, a translation and cultural adaptation was performed with the forward-backward method [85].

Posttraumatic Diagnosis Scale (PDS-F)

Maternal PTSD is measured using this 17-items scale based on DSM-IV criteria. Mothers will rate frequency and severity of symptoms, such as re-experiencing, avoidance and hyperarousal, experienced over the last month, and graded on a four-point Likert scale. The PDS displays good psychometric properties [86], and a French version has been validated [87].

Parental Stressor Scale: Neonatal Intensive Care Unit (F-PSS: NICU)

This questionnaire was translated into French and assesses parental stress with 31 items focusing on their perception of stress factors during the NICU stay of their neonate and explores three domains: impact of the visual and auditory environment, behaviour and aspect of the neonate, and parental role [88]. Good psychometric properties have been reported [88].

Parenting Stress Index-Short form (PSI-SF)

This 36-items questionnaire is a shortened version of the *Parental Stress Index* [89], which measures the stress related to parenthood, and is intended for parents of children 0 to 3 years. The three subscales investigate

parental distress, dysfunctional interactions between the parents and the child, and child difficulties. Its validity has been demonstrated in studies of parents of preterm neonates [90]. In this study, the validated French version will be used [91].

Hospital Anxiety and Depression Scale (HADS)

Anxiety and depression symptoms are assessed using the French version of the HADS, which includes 14 items, and measures the severity of symptoms [92]. This questionnaire has good psychometric properties [93].

Edinburgh Postnatal Depression Scale (EPDS)

Maternal depression symptoms will also be assessed with the EPDS, which focuses on the symptoms experienced over the last 7 days [94]. The French version displays good psychometric characteristics [95].

Mother-to-Infant Bonding Scale (MIBS)

In this questionnaire, the mother rates (from 0 to 5) eight adjectives describing her feelings toward her infant, which is indicative of mother-infant bonding [96 97] and was translated into French with good psychometric properties [98].

Infant Behaviour Questionnaire – Revised (IBQ-R) Very Short Form

Infant temperament is assessed through the French version of this questionnaire (total of 191 items). The parent reports on a 7-points Likert scale the frequency of his infant's behaviours during the previous two weeks [99]. Good psychometric properties haven reported [99].

Modified Medical Outcomes Study Social Support Survey (mMOS-SS)

This validated self-reported evaluation consisting of eight items measuring different aspects of social support [100] is based on the 19-items questionnaire assessing the dimensionality of four functional support scales (emotional/informative, tangible, affectionate, and positive social interaction)

[101]. A French translation and cultural adaptation was performed using the forward-back method [85].

Questionnaire of satisfaction and acceptability of the intervention

This questionnaire comprises a general question on maternal satisfaction with the intervention and six questions on its setting, value and usefulness, which will provide a qualitative evaluation. In addition, three questions focus on the acceptability of the intervention by the mothers.

Demographic and perinatal characteristics

Mothers will also report demographic information, including socio-economic status, level of education [102], and previous psychiatric disorder. Neonatal characteristics will be collected from the medical record on severity of morbidity (GA and weight at birth, Apgar score, complications – need for mechanical ventilation and respiratory morbidity, sepsis, and cerebral lesions), as well as the Clinical Risk Index for Babies (CRIB) [103], which represents neonatal morbidity severity.

Assessment of maternal sensitivity and responsiveness

Maternal sensitivity will be assessed at 6 months CA by coding a session of free play between the mother and her infant with the *Emotional Availability Scales* (EAS) [104]. Six domains are evaluated, of which four relate to the mother's behaviour (sensitivity, structuration, intrusion, and hostility toward the infant), and two to the infant's behaviour (reactivity to the mother and maternal involvement). Patterns of interaction and emotional availability can therefore be measured on separate scales [105].

A second tool, the *Care Index* [106], will measure maternal sensitivity, by assessing the interactive behaviour within the mother-infant dyad according to seven scales (facial expressions, vocalizations, posture, expressed affection, turn-taking, control and activity). Three maternal (sensitive, controlling, passive) and four infant (cooperative, compulsive-compliant, demanding, passive) characteristic behaviors are coded on each scale.

Neurodevelopmental assessment of the infant

A standardized neurodevelopmental assessment will be conducted at 6 months CA by a developmental paediatrician, using the Bayley Scales of Infant Development, 3rd Edition [107], which entails three subscales (cognitive, language and motor) with a normative mean score of 100 ± 15 SD.

Sample size calculation

Power calculation (G*Power)[108] based on published means and standard deviations [47 52] related to perceived parental self-efficacy in a sample of preterm (M = 58.51, SD = 12.57) and of term-born (M = 65.9, SD = 8.2) neonates showed that 68 participants would need to be recruited (α = 0.05, 1-β = 0.80, unilateral hypothesis). This is based on the assumption that parental self-efficacy in mothers of preterm babies in the intervention group who benefitted from the intervention would be comparable to that in mothers of term babies. Therefore, it is planned that 80 mothers will be enrolled to anticipate possible participant withdrawal.

STATISTICAL ANALYSES

For the primary outcome regarding the difference in the perceived maternal self-efficacy between the intervention and control groups, linear regression analysis will be employed, with maternal self-efficacy at 1 month as the dependent variable and group as the explanatory variable, with adjustment for baseline maternal self-efficacy. For secondary analyses, linear mixed model regressions will be conducted, with maternal self-efficacy at 1 and 6 months as dependent variables and group, time, and the interaction group x time as independent variables, adjusted for baseline maternal self-efficacy. The sample principle will be applied to all other secondary outcomes. We will include potential confounding variables, if necessary. These include maternal age, sex of the children, and socioeconomic status where applicable. For confirmatory analyses, a Bonferroni correction for multiple analyses will be applied. For initial exploratory analyses, no such correction will be used [109].

Differences between groups will be adjusted for the respective baseline values in case they differ using potential confounding variables, if necessary. These include maternal age, sex of children, and socioeconomic status where applicable. Variables will be transformed if residuals are not normally distributed.

ADVERSE EVENTS

Expected and unexpected adverse events will be recorded during the study period. As the intervention does not involve medical or pharmaceutical treatment, the risk that an adverse event would occur is low. A child psychiatrist will be available for clinical assessment and follow-up if needed, particularly if significant psychological distress or psychiatric illness of the mother or her infant is detected during study participation.

DATA MANAGEMENT

All study data will be coded and entered by research staff (psychology assistant). The database will be regularly updated by the IT Service of the Lausanne University Hospital. Double data entry will be done for the primary outcomes. For the rest of the data, a random 5% will be double-checked. The principal investigator, the co-investigators and the statistician will have access to the final trial dataset. Individual participant data collected during the trial (after deidentification) on which publications from JOIN consortium are based will be available on reasonable request.

ETHICS AND DISSEMINATION

The local ethical committee (Commission d'Ethique du Canton de Vaud, Switzerland, study number: 496/12) approved the study protocol. Little to no risk is expected by participation of the mothers and their neonates in the trial. Signed informed consent will be obtained from all participating mothers. Participation in the study will not interfere with the typical care patients receive after childbirth and during NICU stay. Results from the study will be disseminated at national and international conferences, and in peer-reviewed journals. This randomized controlled trial is registered in *clinicaltrials.gov* (NCT02736136).

SIGNIFICANCE AND OUTLOOK

This study might result in an evidence-based early intervention aimed at reinforcing parental competences, in particular at increasing perceived parental self-efficacy. It would represent a brief, easily accessible, and safe early intervention, which could be implemented in the routine care in the NICU, thus leading to

significant changes in clinical practice. It will also help to characterize the relationships between perceived parental self-efficacy, maternal mental health, maternal perception of their relationship with their infant and their infant's temperament, and maternal sensitivity.

Due to its interdisciplinary nature, this research is of interest for clinicians, educators and researchers in the field of paediatrics and development, psychology, child psychiatry, and public health.

PATIENTS AND PUBLIC INVOLVEMENT

In the early 2000's, the joint observation was introduced in our NICU by two professionals as part of the care of the parent-infant dyads [74]. Due to positive feedback from the parents, the intervention was more routinely performed and systematized to the point that a randomized controlled trial was needed to examine its validity.

Although patients and caregivers' feedback was considered in designing and adapting the intervention, they were not directly involved in the design or recruitment

of this study. However, results will be disseminated in written form to the participants and distributed to the public via social media and public events.

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AUTHOR CONTRIBUTIONS

AH and NF designed the study with input from all other members of the consortium. AB and MMH designed the intervention with input from members of the consortium. JS and AH drafted the manuscript and contributed equally to the present version. AB, MMH, NF, CT, AL and JFT significantly contributed to the establishment and refinement of study procedures and critically revised the manuscript. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

None declared.

ETHICAL APPROVAL

Ethical approval was granted by the Human Research Ethics Committee of the Canton de Vaud (study number 496/12).

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Table 1

Measures	Questionnaires	T1 Baseline	T2 One month post-intervention	T3 Follow-up at 6 months CA
Perceived maternal self-efficacy	PMP-SE	x	x	x
Maternal well-being	PDS-F	x	x	x
	F-PSS NICU	x	x	
	PSI	x	x	x
	HADS	x	x	x
	EPDS	x	x	x
Mother-infant relationship	MIBS	x	x	x
Maternal perception of her infant's temperament	IBQ-R	x	x	x
Maternal sensitivity				x
Maternal satisfaction	Satisfaction questionnaire		x	
Perceived social support	mMOS-SS	x	x	x
Perinatal risk severity	CRIB	x		
Neurodevelopmental assessment	BSID-III			x

Table 1 summarizes the measures at the 3 different time-points.

Abbreviations: CA: corrected age; PMP-SE: Perceived Maternal Self-Efficacy; PDS-F: Posttraumatic Diagnosis Scale; F-PSS NICU: Parental Stressor Scale Neonatal Intensive Care Unit; PSI: Parental Stress Index; HADS: Hospital Anxiety and

Depression Scale; EPDS: Edinburgh Postnatal Depression Scale; MIBS: Mother-to-Infant Bonding Scale; IBQ-R: Infant Behavior Questionnaire-Revised; mMOS-SS: Modified Medical Outcomes Study Social Support Survey; CRIB: Clinical Risk Index for Babies; BSID-III: Bayley Scales of Infant Development, 3rd Edition

Figure legend:

Figure 1: Flow-chart of the study. Abbreviations: CA: corrected age

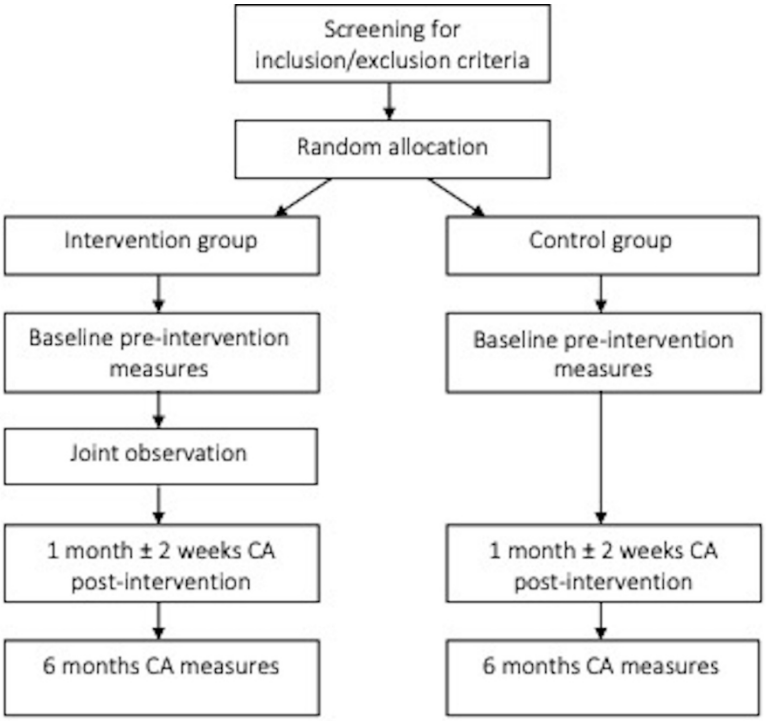

Figure 1: Flow-chart of the study. Abbreviations: CA: corrected age

159x114mm (300 x 300 DPI)

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	4
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	n/a
	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	n/a
	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)	n/a

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	8-11
	6b	Explanation for choice of comparators	13-14
Objectives	7	Specific objectives or hypotheses	12
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)	13
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	13
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)	13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11, 14, Table 1, Figure 1
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
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	14-15
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)	15-16, Table 1, Figure 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	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
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	13
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	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	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 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	15-20
	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	n/a

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	21
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	20-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
	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)	21
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	n/a
	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	n/a
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21-22
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)	21-22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, 21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13, 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	13, 21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
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
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	n/a
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	21-22
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	upon request
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

*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.

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JOINT OBSERVATION IN NICU (JOIN): STUDY PROTOCOL OF A CLINICAL RANDOMIZED CONTROLLED TRIAL EXAMINING AN EARLY INTERVENTION DURING PRETERM CARE

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Mental health
Keywords:	early intervention, preterm, developmental care, self-efficacy, parenting, mother

JOINT OBSERVATION IN NICU (JOIN): STUDY PROTOCOL OF A CLINICAL RANDOMIZED CONTROLLED TRIAL EXAMINING AN EARLY INTERVENTION DURING PRETERM CARE

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KEYWORDS

Early intervention, preterm, neonate, developmental care, self-efficacy, parenting, infant development, mother

WORD COUNT

4248 words, excluding abstract, acknowledgements, author contribution, and references

ABSTRACT

Introduction

Preterm birth may generate significant distress among the parents, who often present with difficulties in appropriating their parental role. Parental stress and low perceived parental self-efficacy may interfere with the infant's socioemotional and cognitive development, particularly through disrupted parent-infant interactions. Perceived parental self-efficacy represents the belief of efficacy in caring for one's own infant and successful incarnation of the parental role, as well as the perception of one's own abilities to complete a specified task. Interventions to support parental role, as well as infant development, are needed, and parental self-efficacy represents a useful indicator to measure the effects of such early interventions.

Methods and analysis

This study protocol describes a randomized controlled trial that will test an early intervention in the NICU (JOIN: Joint Observation In Neonatology) carried out by an interdisciplinary staff team. Mothers of preterm neonates born between 28 and

32 6/7 weeks of gestational age are eligible for the study. The intervention consists of a videotaped observation by a clinical child psychologist or child psychiatrist and a study nurse of a period of care delivered to the neonate by the mother and a NICU nurse. The care procedure is followed by an interactive video guidance intended to demonstrate the neonate's abilities and resources to his parents.

The primary outcome will be the difference in the perceived maternal self-efficacy between the intervention and control groups assessed by self-report questionnaires. Secondary outcomes will be maternal mental health, the perception of the parent-infant relationship, maternal responsiveness, and the neurodevelopment of the infant at 6 months corrected age.

Ethics and dissemination

Ethical approval was granted by the Human Research Ethics Committee of the Canton de Vaud (study number 496/12). Results from this study will be disseminated at national and international conferences, and in peer-reviewed journals.

Trial registration number

clinicaltrials.gov (NCT02736136)

ABBREVIATIONS

BSID-III: Bayley Scales of Infant Development, 3rd Edition / CA: corrected age / CRIB: Clinical Risk Index for Babies / EAS: Emotional Availability Scales / EPDS: Edinburgh Postnatal Depression Scale / F-PSS NICU: Parental Stressor Scale Neonatal Intensive Care Unit / GA: Gestational Age / HADS: Hospital Anxiety and Depression Scale / IBQ-R: Infant Behavior Questionnaire-Revised / MIBS: Mother-to-Infant Bonding Scale / mMOS-SS: Modified Medical Outcomes Study Social Support Survey / NICU: Neonatal Intensive Care Unit / PDS-F: Posttraumatic Diagnosis Scale / PMP-SE: Perceived Maternal Self-Efficacy / PSI: Parental Stress Index / PTSD: Post-Traumatic Stress Disorder

ARTICLE SUMMARY

Strengths and limitations of this study

- The study will test the effects of an early intervention carried out by an interdisciplinary partnership between NICU nurses and clinical child psychologists/ child psychiatrists.

- Among other objectives, the intervention aims at increasing perceived parental self-efficacy in mothers of very preterm infants.
- The intervention draws on theories of neonatal and infant development, as well as interactive video guidance.
- Methodological rigour, including concealment of random allocation and prospective trial registration and publication, limits risk of bias.
- Unblinded participants and clinicians, as well as contamination due to improvement of usual care by health care providers, may increase the risk of bias.

INTRODUCTION

Advances in Neonatal Care

Improvement of pre- and postnatal care over the past decades has led to increased survival of very preterm neonates born less than 32 weeks' gestation [1]. Among others, protective measures to promote health and subsequent neurodevelopment have been developed, including optimization of nutritional support, better characterization of neonatal stress, and improved pain management. In the same perspective, developmental care was introduced in the Neonatal Intensive Care Units (NICU) since the 90's with the intention of minimizing the adverse consequences of prematurity on the developing brain. During a critical period of development, the preterm brain is highly vulnerable to injury, represented by cerebral haemorrhage and insult to the white matter. Additionally, beyond the injury, preterm neonates are prone to alteration of brain maturation with disruption of normal developmental trajectory of both grey and white matters [2-4].

Developmental Care

Over the last two decades, a growing body of research focused on the impact of excessive stimuli such as sound, light, touch or pain on the preterm neonate, hypothesizing that an unfavourable and stressful environment may add to the adverse effects of neonatal morbidity [5]. These concerns led progressively to the introduction of developmental care, which consists of individualized strategies mainly based on the neonate's skills and/or difficulties [6], and supporting the neonate's regulation and development. The first aim of the developmental care is to limit exposure to deleterious environmental stimulations. Management of sensorial dystimulation, as well as of pain and stress during invasive care procedures, represents a central target of developmental care [7 8]. The second main objective focuses on the child's well-being through the adaptation of the sensorial environment in order to provide more physiological external stimuli (tactile, auditory, visual, vestibular), that will help to promote behaviors and postures fostering comfort and regulation. The third objective of the developmental care aims to support parents in their role and to strengthen the relationship they are developing with their child [7 9 10]. Although studies have found contradictory results [11-13], some evidence shows a positive impact of developmental care on short- and long-term neonatal and

neurodevelopmental outcomes [14-19]. Taken together, the different aspects of developmental care aim to build support around the neonate and the family, leading to the development of "family-centered care", with specific recommendations for its implementation in the NICU[20-22].

Impact of prematurity on parents' well-being

Preterm birth and caring for a preterm infant may be distressing for parents, who often feel vulnerable and incompetent in the high-tech NICU environment [23-25]. Parents may present with difficulties in understanding and capturing subtle cues from their infant [26]. Parents show important signs of stress [27], and require more support during the first year after the preterm birth compared with parents of term infants [28]. They may also experience mental health symptoms, including posttraumatic stress disorder (PTSD) [29-35], anxiety, and depression [25 36].

Although the hospitalization of a preterm neonate may affect both parents equally [36], most of the studies examining parental emotional distress so far focused on mothers' experience and needs [24 37 38]. After birth, the mother normally initiates specific behaviors towards her newborn, aimed at supporting the neonate who

experiences high levels of stress during hospitalization in the NICU [39], and at fostering the infant's socioemotional development [40 41]. However, mothers of preterm infants may present difficulties in developing these protective behaviours [42]. Thus, parental stress may interfere with the infant's socioemotional and cognitive development, and is associated with more difficulties in building positive parent-infant relationships due to disrupted interactions [40 43 44]. However, a recent meta-analysis showed that mothers of preterm children were not less sensitive or responsive toward their children than mothers of full-term children [45].

Perceived parental self-efficacy

Perceived parental self-efficacy is defined as 'beliefs or judgements a parent holds of their capabilities to organize and execute a set of tasks related to parenting a child'[46]. Self-efficacy includes two separate notions; first, the belief of efficacy in caring for one's own child across several varied domains of functioning and successful incarnation of the parental role (general self-efficacy) [47-49] , and secondly, the perception of one's own abilities to complete a specified task within a specific

domain (specific self-efficacy) [50]. The present study will focus on the specific self-efficacy, which appears to drive actions and predicts parents' behaviors [48 51].

As demonstrated in previous studies, perceived parental self-efficacy appears to mediate the relationship between psychosocial risk factors and maternal competences [52 53]. Thus, a perception of low self-efficacy is associated with parental depression [52 54-57], high levels of parenting stress [58 59], low family support [60], poor infant health [59 61], and demanding infant temperament [62 63]. In contrast, a perception of high self-efficacy is associated with sensitive and receptive parental behavior, and is related to improved infant socioemotional development [56 64].

Parents of preterm neonates face a complex challenge. While they might be responsive to their infant cues, preterm neonates might not be capable of engaging in sustained and responsive interaction, as they tend to be less attentive and reactive due to immaturity, and to show more negative behaviors and emotions, as well as less rewarding interactions than their term-born peers [56 65-67]. In parallel, mothers of preterm neonates, who are at risk of experiencing depression, anxiety or post-traumatic disorder [25 35], may not be able to interact as adequately with their child, and could be less sensitive than mothers without mental health symptoms.

Mothers of preterm infants may be at a higher risk of decreased maternal confidence [68], although the limited evidence available so far is mixed [57 69]. The quality of care provided by parents is strongly influenced by the maternal perception of self-efficacy, and interventions promoting this may therefore help to increase parenting quality [49 70].

To date, only few early interventions have focused on enhancing perceived parental self-efficacy. The interventions that are currently available in the early neonatal period mainly aim to decrease parental trauma and stress-related symptoms, and to improve parental responsiveness within the parent-infant interaction [10 23 71-73]. Thus, a recent meta-analysis identified only two interventions intended to increase perceived maternal self-efficacy [74-76]. These two interventions concentrated on different techniques of parenting education, and one of the two demonstrated improved cognitive child development at 4 months of age [76]. The present study focuses on the joint observation, which is an interdisciplinary intervention performed in the NICU soon after birth. The main aim of the study is to examine whether this early intervention increases perceived parental self-efficacy.

Joint observation

The joint observation (JOIN: Joint Observation In Neonatology [77]) was developed in line with the three objectives of the developmental care model. This early intervention program in the NICU is carried out by an interdisciplinary partnership of professionals, thereafter called observers, including NICU nurses, paediatricians, clinical child psychologists or child psychiatrists. They all received a 20 hours training, delivered by the same experienced clinical child psychologist (AB) for consistency, and participate in regular supervision sessions during the study period.

The intervention combines elements issued from four distinct theories of neonatal and infant development. First, the evaluation of neonatal behaviour developed by Brazelton and Nugent [78] underlines the importance of parents detecting the neonate's competences and fragilities, and interpreting stress cues to adjust to the infant's regulation needs. Second, the synactive model of AIs [79] proposes a program of individualized care avoiding overstimulation in the NICU and supporting the neonate's self-regulation and competences. Third, the sensorimotor approach elaborated by Bullinger [80] consists mainly of the assessment of sensory

dystimulations provided to the neonate, and the management of subsequent tonico-postural disturbances observed during the NICU stay with the long-term perspective of optimizing the infant's development. This approach builds a framework to adjust the care procedures to the neonate's capacity to treat multisensory information, and to reach a sensoritonic balance that allows and supports interactive behaviours.

Fourth, the interactive guidance is a model based on the observation and analysis of parent-infant interactions trough the therapeutic use of video-feedback [81-83]. This approach aims to allow parents to become aware of their competences and resources, as well as the skills and needs of their infant. Video-feedback has recently been studied as an intervention in the NICU [84 85]. The authors postulated that the interactive guidance through video-feedback reduces the negative impact of preterm birth on the parent-infant relationship, and the behavioural withdrawal of the parent. The results of this previous work have revealed increased parental sensitivity and positive effects on the developing relationship [84]. A randomized clinical study implementing video-feedback not only during the NICU stay, but also during the first year of life specifically demonstrated positive effects on parents of preterm infants

with a lowering of mothers' post-traumatic stress symptoms and enhancement in maternal sensitivity and quality of mother-infant interactions[86].

In order to address the main objective, the present intervention is focusing on following areas: 1) The neonate's adaptive capacity and competences are highlighted, as well as interactive signals, in order to promote parents' emotional involvement, awareness of the infant's perspective, resources, and needs. For instance, the neonate's interactive initiatives, as well as the responses to parental touch and/or voice, such as eye opening or head turning, will be highlighted. 2) To reinforce parental responsiveness, the parent's behaviors that are supporting the neonate's signals are pointed out during the video extracts, highlighting the parental relational competences frequently unidentified by the parents themselves. For example, positive emotional interactions between the mother and her neonate will be emphasized, such as adapting the voice and facial expression in order to support the neonate's alertness. 3) With the aim of developing individualized care, measures can be suggested acknowledging the specificities of each neonate (sensorial irritability, tonico-postural disturbances or withdrawal for instance), and adjusting the care to reinforce the neonate's own capacity of auto-regulation and to support

sensoritonic balance development in a long-term perspective. For instance, the parent's gestures of support according to the baby's tonico-postural needs will be identified, such as supporting the baby's neck or pelvis during the interaction or adjusting the rhythm to help the neonate developing auto-regulation competencies.

The joint observation pragmatically consists of two phases. Firstly, a video-recorded period of routine care for the preterm neonate (such as a nappy change) is carried out by both the parent (mostly the mother) and a NICU nurse for a duration of approximately 30 minutes.

There is no intervention by the observers during the videotaping. Secondly, before gathering with the mother, several short extracts of the period of care are carefully selected by the observers in order to reach the objectives of the intervention. During the discussion and for illustration purpose, the observers will play back 4-6 short extracts of 10-30 seconds each to the parents, showing short specific moments of interactive behaviors that usually escape awareness. This video-feedback, which lasts about 60 minutes, is conducted in order to point out the quality of the relational and emotional parent-infant interactions, and highlights moments of attunement, adjustment, synchrony, reciprocity, and mutuality.

Aims of the present study

The objectives of the present study are to measure the effects of the joint observation as an early intervention performed in the NICU on outcomes relative to parental perception and mental health, as well as to indices of the parent-infant relationship quality and of child development. The primary outcome measure will be the perceived maternal self-efficacy. Secondary objectives will be to measure the impact of this intervention on maternal mental health (including perceived stress, post-traumatic stress, anxiety, depression), on maternal perception of the parent-infant relationship, on maternal responsiveness, and on the neurodevelopment of the infant at 6 months corrected age (CA). In addition, acceptability of the intervention and maternal satisfaction will be assessed.

METHODS AND ANALYSIS

Study Design

We will conduct a monocentric randomized controlled trial testing an intervention compared with treatment-as-usual, in the level III NICU of a Swiss University Hospital.

Study population, recruitment, group allocation, and blinding

All mothers of preterm neonates born between 28 and 32 6/7 weeks of gestational age (GA), admitted to the NICU, and aged less than 8 weeks of life are eligible to participate. Exclusion criteria were set for ethical considerations and in order to avoid approaching mothers needing acute treatment, and include the following: maternal age <18 years; established intellectual disability or psychotic illness; insufficient French-speaking level to complete questionnaires due to impossibility to obtain valid translations to multiples languages for financial reasons; and cardio-respiratory instability of the preterm neonate (severe brady-apnea

syndrome, oxygen requirement >30%) to ensure survival during the study period. Regarding twins or triplets, only the first-born neonate or the one being more stable will be included in the study.

Recruitment will be performed by the study nurses, who approach the eligible mothers once their infants are stable enough, i.e., after the critical period of the first week of life when cardio-respiratory stability is established, usually on non-invasive ventilation and with oxygen requirement <30%, which would also permit more active participation of the parents in the neonate's care. The allocation ratio of randomisation is 1:1, using a computer-generated list of random blocks (https://www.sealedenvelope.com/simple-randomiser). The allocation sequence will be concealed from the principal investigator in sequentially numbered, opaque, sealed envelopes. Envelopes will be opened only after the enrolled participants gave signed consent and completed all baseline assessments. The principal investigator and the statistician will be blind to group allocation. All participant data will be coded to ensure confidentiality.

Control group

Participants in the control group will receive treatment-as-usual. They will be asked to complete questionnaires at the same time-points as the participants in the intervention group: at recruitment, at one month after enrolment, and at 6 months of their infant's corrected age (CA). At 6 months CA, a neurodevelopmental assessment of the infant and a 10-min filmed mother-infant interaction will take place.

Intervention group

Mothers assigned to the intervention group will be asked to complete self-report questionnaires at the three time-points described above. The intervention in the form of the joint observation will be planned after enrolment depending on the infant's clinical state and stability. The intervention is two-fold: firstly, the observers are jointly observing a period of care administered to the neonate jointly by her mother and a NICU nurse. The care procedure is video-taped and an observation grid [87] is completed by the observers. Secondly, the mother and the NICU nurse participate in a video-feedback session with the two observers. The discussion is based on the principles of interactive guidance [84], as described above. At the end of

the intervention, the mother will also be asked to complete a questionnaire regarding her satisfaction with the intervention.

At 6 months CA, a neurodevelopmental assessment of the infant and a 10-min filmed mother-infant interaction will be carried out.

Primary outcome

The primary outcome is the difference in perceived maternal self-efficacy between the control and intervention groups measured with the *Perceived Maternal Parenting Self-Efficacy* (PMP-SE) questionnaire one month after study enrolment.

Secondary outcomes

Maternal outcomes

Using validated self-reported questionnaires described below, various aspects of maternal well-being will be compared between the two groups at baseline and at the 1-month and 6-month follow-up, including symptoms of PTSD (*Posttraumatic Diagnostic Scale),* parental stress (*Parental Stressor Scale: Neonatal Intensive Care Unit* and *Parenting Stress Index-Short form)*,

anxiety (*Hospital Anxiety and Depression Scale)* and depression *(Edinburgh Postnatal Depression Scale).* Other measures will include maternal perception of the parent-infant relationship *(Mother-to-Infant Bonding Scale)* and of her infant's temperament (*Infant Behaviour Questionnaire – Revised*), perceived social support (*Modified Medical Outcomes Study Social Support Survey)*, and maternal sensitivity or responsiveness (*Emotional Availability Scales* and *Care Index*). In addition, acceptability and maternal satisfaction of the intervention will be assessed in the intervention group.

Neonatal outcomes

The neurodevelopmental outcome of the preterm neonates will be measured at 6 months CA (*Bayley Scales of Infant Development, 3rd Edition [BSID-III]*).

Data collection and visits

After enrolment, mothers will be asked to complete several questionnaires described below, and again one month after study enrolment, and at 6 months CA.

Infants will return at 6 months CA to the neonatal follow-up clinic for the neurodevelopmental assessment and the 10-min filmed mother-infant interaction. The study measures and timings are summarized in Table 1 and Figure 1.

Measures

Self-report questionnaires

Perceived Maternal Parenting Self-Efficacy (PMP-SE)

This questionnaire including 20 items, which represent 4 subscales (care taking procedures, evoking behaviour(s), reading behaviours or signalling, and situational beliefs), was specifically developed for mothers of preterm neonates, and has good psychometric properties [50]. Responses to each item are recorded on a four-point Likert scale (from 'strongly disagree' – score 1 to 'strongly agree' – score 4). To obtain a French version of the questionnaire, a translation and cultural adaptation was performed with the forward-backward method [88].

Posttraumatic Diagnosis Scale (PDS-F)

Maternal PTSD is measured using this 17-items scale based on DSM-IV criteria. Mothers will rate frequency and severity of symptoms, such as re-experiencing, avoidance and hyperarousal, experienced over the last month, and graded on a four-point Likert scale. The PDS displays good psychometric properties [89], and a French version has been validated [90].

Parental Stressor Scale: Neonatal Intensive Care Unit (F-PSS: NICU)

This questionnaire was translated into French and assesses parental stress with 31 items focusing on their perception of stress factors during the NICU stay of their neonate and explores three domains: impact of the visual and auditory environment, behaviour and aspect of the neonate, and parental role [91]. Good psychometric properties have been reported [91].

Parenting Stress Index-Short form (PSI-SF)

This 36-items questionnaire is a shortened version of the *Parental Stress Index* [92], which measures the stress related to parenthood, and is intended for parents of children 0 to 3 years. The three subscales investigate

parental distress, dysfunctional interactions between the parents and the child, and child difficulties. Its validity has been demonstrated in studies of parents of preterm neonates [93]. In this study, the validated French version will be used [94].

Hospital Anxiety and Depression Scale (HADS)

Anxiety and depression symptoms are assessed using the French version of the HADS, which includes 14 items, and measures the severity of symptoms [95]. This questionnaire has good psychometric properties [96].

Edinburgh Postnatal Depression Scale (EPDS)

Maternal depression symptoms will also be assessed with the EPDS, which focuses on the symptoms experienced over the last 7 days [97]. The French version displays good psychometric characteristics [98].

Mother-to-Infant Bonding Scale (MIBS)

In this questionnaire, the mother rates (from 0 to 5) eight adjectives describing her feelings toward her infant, which is indicative of mother-infant bonding [99] [100] and was translated into French with good psychometric properties [101].

Infant Behaviour Questionnaire – Revised (IBQ-R) Very Short Form

Infant temperament is assessed through the French version of this questionnaire (total of 191 items). The parent reports on a 7-points Likert scale the frequency of his infant's behaviours during the previous two weeks [102]. Good psychometric properties haven reported [102].

Modified Medical Outcomes Study Social Support Survey (mMOS-SS)

This validated self-reported evaluation consisting of eight items measuring different aspects of social support [103] is based on the 19-items questionnaire assessing the dimensionality of four functional support scales (emotional/informative, tangible, affectionate, and positive social interaction)

[104]. A French translation and cultural adaptation was performed using the forward-back method [88].

Questionnaire of satisfaction and acceptability of the intervention

This questionnaire comprises a general question on maternal satisfaction with the intervention and six questions on its setting, value and usefulness, which will provide a qualitative evaluation. In addition, three questions focus on the acceptability of the intervention by the mothers.

Demographic and perinatal characteristics

Mothers will also report demographic information, including socio-economic status, level of education [105], and previous psychiatric disorder. Neonatal characteristics will be collected from the medical record on severity of morbidity (GA and weight at birth, Apgar score, complications – need for mechanical ventilation and respiratory morbidity, sepsis, and cerebral lesions), as well as the Clinical Risk Index for Babies (CRIB) [106], which represents neonatal morbidity severity.

Assessment of maternal sensitivity and responsiveness

Maternal sensitivity will be assessed at 6 months CA by coding a session of free play between the mother and her infant with the *Emotional Availability Scales* (EAS) [107]. Six domains are evaluated, of which four relate to the mother's behaviour (sensitivity, structuration, intrusion, and hostility toward the infant), and two to the infant's behaviour (reactivity to the mother and maternal involvement). Patterns of interaction and emotional availability can therefore be measured on separate scales [108].

A second tool, the *Care Index* [109], will measure maternal sensitivity, by assessing the interactive behaviour within the mother-infant dyad according to seven scales (facial expressions, vocalizations, posture, expressed affection, turn-taking, control and activity). Three maternal (sensitive, controlling, passive) and four infant (cooperative, compulsive-compliant, demanding, passive) characteristic behaviors are coded on each scale.

Neurodevelopmental assessment of the infant

A standardized neurodevelopmental assessment will be conducted at 6 months CA by a developmental paediatrician, using the Bayley Scales of Infant Development, 3rd Edition [110], which entails three subscales (cognitive, language and motor) with a normative mean score of 100 ± 15 SD.

Sample size calculation

Power calculation (G*Power)[111] based on published means and standard deviations [50 55] related to perceived parental self-efficacy in a sample of preterm (M = 58.51, SD = 12.57) and of term-born (M = 65.9, SD = 8.2) neonates showed that 68 participants would need to be recruited (α = 0.05, 1-β = 0.80, unilateral hypothesis). This is based on the assumption that parental self-efficacy in mothers of preterm babies in the intervention group who benefitted from the intervention would be comparable to that in mothers of term babies. Therefore, it is planned that 80 mothers will be enrolled to anticipate possible participant withdrawal.

STATISTICAL ANALYSES

For the primary outcome regarding the difference in the perceived maternal self-efficacy between the intervention and control groups, linear regression analysis will be employed, with maternal self-efficacy at 1 month as the dependent variable and group as the explanatory variable, with adjustment for baseline maternal self-efficacy. For secondary analyses, linear mixed model regressions will be conducted, with maternal self-efficacy at 1 and 6 months as dependent variables and group, time, and the interaction group x time as independent variables, adjusted for baseline maternal self-efficacy. The sample principle will be applied to all other secondary outcomes. We will include potential confounding variables, if necessary. These include maternal age, sex of the children, and socioeconomic status where applicable. For confirmatory analyses, a Bonferroni correction for multiple analyses will be applied. For initial exploratory analyses, no such correction will be used [112].

Differences between groups will be adjusted for the respective baseline values in case they differ using potential confounding variables, if necessary. These include maternal age, sex of children, and socioeconomic status where applicable. Variables will be transformed if residuals are not normally distributed.

PATIENTS AND PUBLIC INVOLVEMENT

In the early 2000's, the joint observation was introduced in our NICU by two professionals as part of the care of the parent-infant dyads [77]. Due to positive feedback from the parents, the intervention was more routinely performed and systematized to the point that a randomized controlled trial was needed to examine its validity.

Although patients and caregivers' feedback was considered in designing and adapting the intervention, they were not directly involved in the design or recruitment of this study. However, results will be disseminated in written form to the participants and distributed to the public via social media and public events.

ADVERSE EVENTS

Expected and unexpected adverse events will be recorded during the study period. As the intervention does not involve medical or pharmaceutical treatment, the risk that an adverse event would occur is low. A child psychiatrist will be available for clinical assessment and follow-up if needed, particularly if significant psychological

distress or psychiatric illness of the mother or her infant is detected during study participation.

DATA MANAGEMENT

All study data will be coded and entered by research staff (psychology assistant). The database will be regularly updated by the IT Service of the Lausanne University Hospital. Double data entry will be done for the primary outcomes. For the rest of the data, a random 5% will be double-checked. The principal investigator, the co-investigators and the statistician will have access to the final trial dataset. Individual participant data collected during the trial (after deidentification) on which publications from JOIN consortium are based will be available on reasonable request.

ETHICS AND DISSEMINATION

The local ethical committee (Commission d'Ethique du Canton de Vaud, Switzerland, study number: 496/12) approved the study protocol. Little to no risk is expected by participation of the mothers and their neonates in the trial. Signed

informed consent will be obtained from all participating mothers. Participation in the study will not interfere with the typical care patients receive after childbirth and during NICU stay. Results from the study will be disseminated at national and international conferences, and in peer-reviewed journals. This randomized controlled trial is registered in *clinicaltrials.gov* (NCT02736136).

SIGNIFICANCE AND OUTLOOK

This study might result in an evidence-based early intervention aimed at reinforcing parental competences, in particular at increasing perceived parental self-efficacy. It would represent a brief, easily accessible, and safe early intervention, which could be implemented in the routine care in the NICU, thus leading to significant changes in clinical practice. It will also help to characterize the relationships between perceived parental self-efficacy, maternal mental health, maternal perception of their relationship with their infant and their infant's temperament, and maternal sensitivity.

Due to its interdisciplinary nature, this research is of interest for clinicians, educators and researchers in the field of paediatrics and development, psychology, child psychiatry, and public health.

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AH and NF designed the study with input from all other members of the consortium. AB and MMH designed the intervention with input from members of the consortium. JS and AH drafted the manuscript and contributed equally to the present version. AB, MMH, NF, CT, AL and JFT significantly contributed to the establishment and refinement of study procedures and critically revised the manuscript. All authors approved the final version of the manuscript.

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COMPETING INTERESTS

None declared.

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Table 1

Measures	Questionnaires	T1 Baseline	T2 One month post-intervention	T3 Follow-up at 6 months CA
Perceived maternal self-efficacy	PMP-SE	x	x	x
Maternal well-being	PDS-F	x	x	x
	F-PSS NICU	x	x	
	PSI	x	x	x
	HADS	x	x	x
	EPDS	x	x	x
Mother-infant relationship	MIBS	x	x	x
Maternal perception of her infant's temperament	IBQ-R	x	x	x
Maternal sensitivity				x
Maternal satisfaction	Satisfaction questionnaire		x	
Perceived social support	mMOS-SS	x	x	x
Perinatal risk severity	CRIB	x		
Neurodevelopmental assessment	BSID-III			x

Table 1 summarizes the measures at the 3 different time-points.

Abbreviations: CA: corrected age; PMP-SE: Perceived Maternal Self-Efficacy; PDS-F: Posttraumatic Diagnosis Scale; F-PSS NICU: Parental Stressor Scale Neonatal Intensive Care Unit; PSI: Parental Stress Index; HADS: Hospital Anxiety and

Depression Scale; EPDS: Edinburgh Postnatal Depression Scale; MIBS: Mother-to-Infant Bonding Scale; IBQ-R: Infant Behavior Questionnaire-Revised; mMOS-SS: Modified Medical Outcomes Study Social Support Survey; CRIB: Clinical Risk Index for Babies; BSID-III: Bayley Scales of Infant Development, 3rd Edition

Figure legend:

Figure 1: Flow-chart of the study. Abbreviations: CA: corrected age

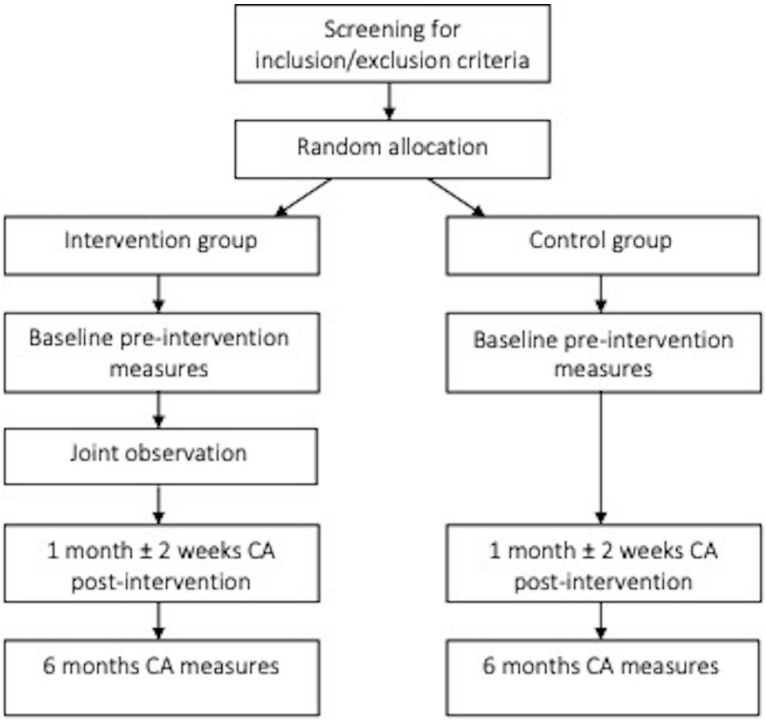

Figure 1: Flow-chart of the study. Abbreviations: CA: corrected age

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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	4
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	23
	5b	Name and contact information for the trial sponsor	n/a
	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	n/a
	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)	n/a

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	8-11
	6b	Explanation for choice of comparators	13-14
Objectives	7	Specific objectives or hypotheses	12
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)	13
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	13
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)	13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11, 14, Table 1, Figure 1
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
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	14-15
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)	15-16, Table 1, Figure 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	20
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13
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	13
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	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	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 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	15-20
	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	n/a

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	21
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	20-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
	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)	21
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	n/a
	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	n/a
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	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21-22
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)	21-22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, 21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13, 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	13, 21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
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
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	n/a
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	21-22
	31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	upon request
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

*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.