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Complete List of Authors:	Ghetti, Claire; University of Bergen, GAMUT, The Grieg Academy - Dept. of Music Bieleninik, Łucja; Uni Research AS, Uni Research Health, GAMUT; Uniwersytet Gdanski, Institute of Psychology Hysing, Mari; Uni Research AS, Uni Research Health, Regional Centre for Child and Youth Mental Health and Child Welfare Kvestad, Ingrid; Uni Research AS, Uni Research Health, Regional Center for Child and Youth Mental Health and Child Welfare Assmus, Jörg; Uni Research AS, Uni Research Health, GAMUT Romeo, Renee; KCL, Ettenberger, Mark; Hospital Universitario de la Fundacion Santa Fe de Bogota; SONO – Centro de Musicoterapi Arnon, Shmuel; Meir Medical Center, Neonatal Department; Tel-Aviv University, Sackler School of Medicine Söderström Gaden, Tora; Uni Research AS, Uni Research Health Gold, Christian; Uni Research Health Bergen, Uni Research Health
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Longitudinal Study of music Therapy's Effectiveness for Premature infants and their caregivers (LongSTEP): protocol for an international randomized trial

Authors: Claire Ghetti†*, Łucja Bieleninik†, Mari Hysing, Ingrid Kvestad, Jörg Assmus, Renee Romeo, Mark Ettenberger, Shmuel Arnon, Tora Söderström Gaden, Christian Gold†
†Equal contributors

***Address correspondence to:** Claire Ghetti, GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Postbox 7805, 5020 Bergen, Norway. Email: claire.ghetti@uib.no. Phone: +47-465 08 095.

Affiliations:
Claire Ghetti, PhD, GAMUT, The Grieg Academy – Dept. of Music, University of Bergen, Bergen, Norway
GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Postbox 7805, 5020 Bergen, Norway; Email: claire.ghetti@uib.no

Łucja Bieleninik, PhD, GAMUT, Uni Research Health, Uni Research, Bergen, Norway; Institute of Psychology, University of Gdańsk, Poland
GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Postbox 7805, 5020 Bergen, Norway; Email: lucja.bieleninik@uni.no

Mari Hysing, PhD, PsyD, Regional Center for Child and Youth Mental Health and Child Welfare, Uni Research Health, Uni Research, Postbox 7810, 5020 Bergen, Norway; Email:mahy@norceresearch.no

Ingrid Kvestad, PhD, PsyD, Regional Center for Child and Youth Mental Health and Child Welfare, Uni Research Health, Uni Research, Postbox 7810, 5020 Bergen, Norway; Email: inkv@norceresearch.no

Jörg Assmus, PhD, GAMUT, Uni Research Health, Uni Research, Bergen, Norway
GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Postbox 7805, 5020 Bergen, Norway; Email: jorg.assmus@uni.no

Renee Romeo, PhD, King's Health Economics, King's College London, Decrespigny Park, London, SE5 8AF, United Kingdom. Email: renee.romeo@kcl.ac.uk

Mark Ettenberger, PhD, University Hospital Fundación Santa Fe de Bogotá; SONO – Centro de Musicoterapi, Bogotá, Colombia; Email: mark.ettenberger@sono.la

Shmuel Arnon, MD, Neonatal Department, Meir Medical Center, Kfar-Saba, 44281, Israel; Sackler School of Medicine, Tel-Aviv University, Israel; Email: harnon@netvision.net.il

Tora Söderström Gaden, GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Postbox 7805, 5020 Bergen, Norway. Email: torasoderstrom@gmail.com

Christian Gold, PhD, GAMUT, Uni Research Health, Uni Research, Bergen, Norway

GAMUT – The Grieg Academy Music Therapy Research Centre, Uni Research Health, Uni Research, Postbox 7805, 5020 Bergen, Norway. Email: christian.gold@uni.no

Authors' contributions:
ŁB, CGh and CGo conceived the study, developed the study design, and drafted the manuscript. JA developed the study design, provided statistical expertise in clinical trial design and is conducting the primary statistical analysis. IK, MH, RR, ME, SA and TG contributed to the study design, with IK and MH contributing in particular the definition of outcomes. All authors contributed to refinement of the study protocol and approved the final manuscript.

Abstract

Introduction: Preterm birth has major medical, psychological and socio-economic consequences worldwide. Music therapy (MT) has positive effects on physiological measures of preterm infants and maternal anxiety, but rigorous studies including long-term follow-up are missing. Drawing upon caregivers' inherent resources, this study emphasizes caregiver involvement in MT to promote attuned, developmentally-appropriate musical interactions that may be of mutual benefit to infant and parent. This study will determine whether MT, as delivered by a qualified music therapist during neonatal intensive care unit (NICU) hospitalization and/or in home/municipal settings following discharge, is superior to standard care in improving bonding between primary caregivers and preterm infants, parent well-being and infant development.

Methods and analysis: *Design:* International multi-center, assessor-blind, 2x2 factorial, pragmatic randomized controlled trial; informed by a completed feasibility study. *Participants:* 250 preterm infants and their parents. *Intervention:* MT focusing on singing specifically tailored to infant responses, will be delivered during NICU and/or during a post-discharge 6-month period. *Primary outcome:* Changes in mother-infant bonding until 6 months corrected age (CA), as measured by the Postpartum Bonding Questionnaire. *Secondary outcomes*: Mother-infant bonding at discharge and over 12 months CA; child development over 24 months; and parental depression, anxiety, and stress, and infant re-hospitalization, all over 12 months.

Ethics and dissemination: The Regional Committees for Medical and Health Research Ethics approved the study (2018/994/REK Nord, 03 July 2018). Service users were involved in development of the study and will be involved in implementation and dissemination. Dissemination of findings will apply to local, national, and international levels.

Discussion: This study fills a gap by measuring the long-term impact of MT for preterm infants/caregivers, and of MT beyond the hospital context. By incorporating family-centered care, continuity of care, user involvement, and cultural relevance, this study may contribute to improved quality of care for premature infants and their parents.

Trial registration: Registered at ClinicalTrials.gov, registration number NCT03564184. Will be registered at HelseNorge.

Keywords: prematurity, preterm neonates, bonding**,** music therapy, non-pharmacological interventions, psychosocial interventions, randomized controlled trial

Strengths and limitations of this study

- Following several studies suggesting short-term effects of MT for premature infants, this study will examine longer-term effects up to two years.
- Parents will be actively included in MT, with the aim of improving outcomes of both infants and parents.
- MT will be continued after discharge from hospital, thus providing a bridge between specialized and primary health care.
- As a multinational trial, results will be relevant across a range of settings in diverse societies that enable social support from families.
- Due to the nature of the intervention, participants cannot be blinded. Similarly, most outcomes cannot be blinded because they rely on parent reports.

Background

The global average rate of preterm birth is around 11% worldwide corresponding to 15 million preterm infants each year [1, 2]. Over one million die as a direct result of prematurity, and another million show lifetime impairments [3]. With improved survival rates, there is growing concern for long lasting complications including mental health problems, cognitive impairments, and poorer quality of life [1, 4-6]. Moreover, the economic burden of preterm birth includes increased cost of neonatal care, long-term costs associated with complex health status, and losses in economic productivity over the lifespan [7].

Premature labor is perceived as a stressful [8] and traumatic [9, 10] event that can interrupt mothers' antenatal bonding [11]. Families of premature infants can experience higher levels of stress, anxiety, and fear for the infant's safety, as well as insecurity and powerlessness [10, 12]. Mothers are at risk for postpartum depression, posttraumatic stress disorder, feelings of guilt, mourning, and lack of self-worth [13]. Fathers experience significant stress, which may extend beyond the acute phase following the infant's birth [14]. Supportive and educational interventions provided to fathers in the acute phase of the infant's hospitalization can empower their fathering ability and reduce paternal stress [15].

Separation due to NICU stay and prolonged hospitalization may complicate the development of healthy parent-infant bonding and in some cases adversely impact the formation of secure attachment [10, 16]. Mother-infant relationship plays a central role in the child's socio-emotional development and formation of future intimate relationships [17, 18]. Mothers' psychological well-being [19] or postpartum depression [20] are important factors affecting parent-infant relationship in the postnatal period. However, even with sensitive parenting, children born very preterm or very low birthweight are at higher risk of demonstrating disorganized attachment than those born full-term, and neurological impairment predicts this disorganized attachment [21]. Involving fathers in infant care,

including skin-to-skin care, during the first days of the infant's life can positively impact the bonding process while improving support to partners [22], and can lead to improved self-esteem, feelings of closeness to the infant, and perception of more equal parenthood [23]. Decreasing maternal stress and reducing early separation during NICU hospitalization may be beneficial for long-term outcomes [24].

MT is part of NICU standard treatment in some hospitals in several countries, but supply is usually limited even where that is the case. MT in infant critical care involves the informed use of music and a therapeutic relationship to promote infant development and facilitate bonding with primary caregivers [25]. MT promotes infant sensory regulation and may contribute to neurological development [26, 27]. Incorporating parents as active partners in implementing MT during the NICU stay has shown to decrease infant and parent distress [28], and may thus promote bonding [29]. MT beneficially impacts infant physiological parameters, behavior state, weight gain and feeding ability, and may reduce hospital stay [26, 30-34]. There are also some indications of a positive impact of music on sleep for premature infants [31, 35, 36]. Incorporating parents as active partners in implementing MT during the NICU stay leads to decreased infant and parent distress [28], and MT provides a culturally-sensitive form of family-centered care that empowers fathers in the care of their premature infants [29]. MT-based consult-to-parent models, such as the *Time Together* adaptation of contingent singing into a parent education program, can help extend benefits to families beyond those most prioritized to receive MT services [37].

In a rigorous systematic review and meta-analysis of randomized controlled trials (RCTs), a large and favorable effect of MT on respiratory rate and maternal anxiety was confirmed [38]; however, several areas require further investigation. Rigorously designed and adequately powered studies using standardized outcome measures and interventions implemented by music therapists with specialized NICU training are required. Parallel RCTs to evaluate long-

term effects of MT, and extending intervention periods past discharge from NICU, are required to assess long-term impact, which is a substantial gap in present knowledge [38]. Studies examining longitudinal provision of MT tailored to different stages of infant development [28] and long-term effects of MT on the development of healthy parent-infant bonding and secure attachment are needed [26, 38].

Building on promising results from phase II studies and meta-analyses, LongSTEP is the first phase III trial worldwide of MT's effectiveness for premature infants and their caregivers. This trial will determine whether MT as delivered by a qualified music therapist during NICU hospitalization and/or after discharge to home is superior to standard care in improving bonding between primary caregivers and preterm infants. This project promotes continuity of care by bridging the transition from hospital to home and uses family-centered developmental care. Conducting the study in several countries with high levels of parental presence in the NICU, provides sufficient sample size to analyze treatment effects. The results will inform the effective use of music therapy across levels of health care for the participating NICUs in Europe, the Middle East, and South America. This study will contribute to an improved understanding of the relation between music and health and will enable evidence-based recommendations for the application of MT in primary health care services.

Objectives

The primary objective of this study is: to provide high-quality evidence of the effects of MT on bonding between preterm infants and their parents during neonatal hospitalization and in primary care post-discharge.

Secondary objectives are as follows:

- To examine effects of MT on premature infants' general and socio-emotional development.
- To examine effects of MT on parents' symptoms of depression, anxiety, and stress.

- To examine medical and social factors of premature infants (sex, GA at birth, hearing status) and their parents (bonding) that may be associated with effects of MT.
- To prepare for examining cost-effectiveness and longer-term evaluation of effects.

We hypothesize that MT during or after NICU, compared to standard care alone, will lead to better parent-infant bonding, which in turn may beneficially impact infant development and parent mental health outcomes. Effects of MT may depend on medical and social factors. Clinical effectiveness may be associated with cost-effectiveness and may be sustained in the longer term.

Methods

Design

The Longitudinal Study of music Therapy's Effectiveness for Premature infants and their caregivers (LongSTEP) is designed as a 2x2 factorial, international, multi-center, assessor-blind pragmatic RCT to evaluate the long-term effect of MT in NICU and/or after discharge on premature infants and their primary caregivers across a 12-month time period (Fig. 1). The factorial design entails a two-phase protocol covering both the stay in the NICU and follow-up care after discharge from hospital, with two randomization time points, and tests the independent effect of each combination: NICU-MT, post-discharge MT, both, or neither, as well as interactions between them.

Pilot testing and user feedback

A feasibility study was conducted at one Norwegian NICU (initiated January 2018) to determine acceptability and suitability of the intervention and study procedures and to obtain parental perspectives in order to inform design of the main study. Pilot testing evaluated feasibility in the areas of participant recruitment, delivery of study conditions, planned assessments, and retention, as well as tracking of treatment occurring as part of standard care.

Following ethics approval, three families at a Norwegian NICU were offered MT 2 times/week during NICU hospitalization and 2 times/month during the first 3 months after discharge home. Follow-up interviews with parents revealed that parents were willing to take part in MT in the NICU and sing for their infants, and that MT offered a break from typical hospital routines and a different way of "reading" and relating to their infants. Parents found the self-report outcome measures acceptable and the nature of participation in MT as well as the frequency of sessions feasible and comfortable. Parents stated they would also have been willing to participate in the study if designed as an RCT despite the chance of being allocated to standard care.

A primary aim of the feasibility study was to determine whether the Postpartum Bonding Questionnaire (PBQ) should be retained as a primary outcome in the subsequent main trial. The PBQ is validated and widely used in the literature [39], but we wished to explore its acceptability and perceived relevance with mothers in the feasibility study. While the full results will be published separately, preliminary analysis from the Norwegian feasibility study revealed that the PBQ scored on relevant items, changed over time, and mothers expressed no particular objections to completing its items. Results from the feasibility study and discussion with parents in our User Advisory Group informed our decision to retain the PBQ as a primary outcome measure for the main study.

The feasibility study also enabled us to test logistical parameters related to post-discharge MT. We provided post-discharge sessions in the home setting, following advice from our User Advisory Group. Even with an inclusion criterion assuring that parents live within "reasonable commuting distance from the treating NICU," the total travel and session time used during a single at-home session ranged from 130 to 180 minutes. It also provided difficult to schedule sessions at a consistent 2 times/month frequency due to schedule conflicts and variations in parents' schedules and obligations. We therefore decided to adopt

the following frequency in the main study to make consistency of sessions more feasible: 2 times during the first month following discharge from the NICU, and 1 time per month thereafter for a total period of 6 months.

Trial procedures

After informed consent and baseline assessment, participants will be randomly assigned to receive either MT plus standard care or standard care alone during their stay at the NICU. The intervention period will start immediately following randomization and will last until the infant's initial discharge from hospital. Participants will be asked to complete the discharge assessments one to two days before discharge to home; for those who are unable to complete them before discharge, assessments will be valid if completed up to one week after discharge. Upon completion of discharge assessments, participants will be randomly allocated to receive either post-discharge MT in home or municipal settings along with standard primary care, or standard primary care alone across a 6-month time period. Standard care may include other early intervention methods of care with the exception of other MT approaches. Participants are free to attend any type of treatment or therapeutic interventions in a post-partum setting, but they will be asked not to attend MT outside the study context through 12 months corrected age (CA; defined as chronological age reduced by number of weeks born preterm [40]). This time frame is sufficient because the hypotheses of the study concern the effects of early MT during NICU or post-discharge; however, the receipt of any MT during the first 24 months CA outside the study will be recorded. Outcomes will be assessed at several time points: at baseline; one to two days before discharge to home (end of MT during NICU); at 6 months CA (end of post-discharge MT; primary endpoint); 12 and 24 months CA (Fig. 1, 2). Treatment fidelity (adherence and competence) will be evaluated by independent raters using video recordings as described further below. The study has been designed in accordance with the SPIRIT 2013 statement (see Additional file 1 for complete checklist). Ethical approval for

the study has been granted by The Regional Committees for Medical and Health Research Ethics (2018/994/REK Nord) and supplemental ethical approval from each participating country will be secured from relevant ethics committees in those countries prior to recruitment.

Settings

To achieve the target sample size, it is necessary to recruit participants from multiple NICUs. Eligible NICUs are located in countries where the culture reflects what could be considered a "social support" society, where parents are consistently present in the NICU. Eligible NICUs also need to have staff possessing the necessary scientific and clinical expertise to conduct the trial. Current partner sites are located across five countries in Europe, the Middle East, and Latin America (Argentina, Colombia, Israel, Norway, Poland), and include eight NICUs (see trial registration data at ClinicalTrials.gov for an updated list). The number of beds in each NICU ranges from 13 to 60.

Eligibility criteria

Participants deemed eligible for the trial will meet the following criteria: *Infants:* Born below 35 weeks GA, of both genders, any ethnicity, from single or multiple pregnancies, who have achieved sufficient medical stability (as determined by medical staff) to start MT, and will likely be hospitalized for longer than 2 weeks from time of recruitment. In multiple pregnancies, only the first-born infant who achieves medical stability will be included and randomized, while remaining siblings can receive the same interventions for ethical and practical reasons. Infant hearing screenings typically take place prior to discharge from the NICU, thus hearing status may not be known at time of study recruitment. Results of infant hearing screening at discharge will be tracked when available, to facilitate follow-up analysis, but infants who test positive for hearing impairments will still be included in data analysis due to the potential for infant and parent benefit despite such sensory impairment. *Primary*

caregivers: One of the parents/caregivers must provide written, site-specific informed consent before any study procedures occur. Primary caregivers should agree to engage in at least 2 of the 3 MT sessions per week during NICU, and/or in 5 of the 7 MT post-discharge sessions. Primary caregivers should live within reasonable commuting distance from the treating NICU and should have sufficient understanding of the respective national language(s) to answer the questionnaire and participate in MT. Parents with a documented mental illness or cognitive impairment that prevents them from being able to complete the study intervention or outcome assessments will be excluded.

Interventions

The MT approach in this study is informed by models previously described and tested, including Creative Music Therapy with premature infants and their parents [26, 41, 42], First Sounds: Rhythm, Breath & Lullaby [31, 43, 44], and other developmentally-appropriate and family-centered approaches to MT with premature infants and their families [27, 45, 46]. Like other MT models [41, 42], it is based on the notion that infants have a capacity to communicate actively [47, 48]. As in some newer models, parents are highly involved and the therapeutic benefit is directed toward infant and parents alike [31, 41, 44, 46]. The approach here thus builds on an emerging consensus, but is more explicit in its adaption to developmental levels and emphasis on infant-parent co-regulation. Furthermore, unlike previous studies [38], MT is extended beyond the tertiary care setting to help with the transition to daily life and municipal care. MT focuses on supporting positive relationship formation within the infant-parent dyad by promoting beneficial co-regulation, and includes psychotherapeutic support of the parents to promote their stabilization, self-regulation, bonding and restorative experience in alignment with trauma-preventive models [44, 49]. Key elements of the MT intervention appear in Table 1.

MT during NICU: Participants will be offered individual MT sessions 3 times/week for approximately 30-40 minutes/session, with a maximum of 27 sessions per infant (assuming a maximum NICU stay of 9 weeks). Time spent in active music making with the infant may be shorter than 30 minutes, depending upon infant readiness, and the remaining portion of the session will be devoted to providing psychotherapeutic support for parents and coaching them in how to use their voices therapeutically with their infants. MT will be provided for eligible infants once they achieve medical stability, usually after 26 weeks postmenstrual age (PMA; defined as GA at birth plus the time since birth [40]). Use of live music will follow recommendations from the American Academy of Pediatrics Committee on Environmental Health [50] and the Consensus Committee on Recommended Design Standards for Advanced Neonatal Care [51], namely that noise levels within the NICU should remain below 45 dB (A weighted), with hourly maximum sound levels (Lmax) < 65 dBA, and no more than 10% of each hour (L10) > 50 dBA. Prior to the first MT session with the infant, the music therapist will meet with the parents to discuss MT and assess aspects that will inform the course of MT including: music preferences and history, cultural values related to music, level of comfort with singing, infant signals and patterns, family strengths and needs, and any challenges and resources that the parents deem relevant. The music therapist will then explain basic elements of the procedures listed below, engage parents in musical demonstration and form a loose plan for how the parents and music therapist will begin MT with the infant. The music therapist will observe the infant during a period of handling (such as during diaper change or transition to parent's arms) in order to become more familiar with the infant's signals and tolerance of stimulation, and parents' modes of responding to the infant. Thereafter, a flexible protocol of procedures matched to infant PMA, familial/cultural preferences, and infant's demonstrated readiness to receive stimulation, will occur as individually-tailored MT sessions at bedside:

From approximately 26 to below 32 weeks PMA, cautious use of sung/toned voice will be the main focus. During MT, the infant may be: held in a static manner by the caregiver (e.g., skin-to-skin care), resting in his/her isolette with the portal door open, or resting in his/her basinet or bed. MT during skin-to-skin care will be encouraged, if skin-to-skin care is part of standard care and the infant tolerates it. The music therapist assesses the infant's needs and behavior state, and if appropriate for the infant, shows caregivers how to use basic touch and positioning (such as caregiver/therapist's hand lightly and statically placed on infant's chest or back, or hands cupped at infant's head and feet) and/or principles of facilitated tucking and midline alignment to promote physical containment, enable behavior state regulation, and prepare the infant for MT. Parents will hold their infant or provide basic touch and/or positioning, and will receive support or demonstration from the music therapist as needed. Using toning or predominantly wordless singing voice matched to infant breathing patterns, facial expressions and movements [41, 42], while monitoring infant behavior state shifts and physiological responses, the music therapist demonstrates how to either pacify the infant to promote sleep or bring the infant to a quiet alert state, depending upon the infant's needs. Specific pitches used may be matched to the pitch of infant vocalizations, if present, or selected to mask environmental noises, and will aim to be comfortably within the parent's vocal range [43]. When appropriate for the infant, simple melodies or songs of kin [31, 43] modified into an infant-appropriate style are matched to infant breathing rate, gesticulations and facial expressions, and engagement/disengagement cues, so that the music remains infant-directed. Caregivers are encouraged to lead the singing/toning as soon as they feel comfortable, while the music therapist simultaneously provides musical and/or coaching support. MT may occur during breastfeeding or other feeding attempts, if the parents desire it and the infant tolerates it, but MT will not occur during painful or sensorially-demanding medical procedures due to the risk of over-stimulation.

From 32 weeks to below 36 PMA, the use of MT centers around cautious use of infant-directed music with expanded sensory experience. This phase applies as soon as the infant demonstrates readiness to receive additional sensory stimulation, but not prior to 32 weeks PMA. Guidelines from the previous phase apply and are developed upon in this phase for infants who are ready for more than pacification. Culturally-relevant, caregiver-preferred songs are modified in an improvisatory manner by caregivers to match infant's breathing rate, engagement/disengagement cues, facial expressions and gesticulations, in order to facilitate a musical interplay between caregiver and infant [41, 42]. This interplay generally moves from more pacifying in nature to more dynamic and interactive as the infant reaches 36 weeks PMA. Musical interplay may include gentle dynamic touch to back of infant's head or along infant's back, depending upon the infant's tolerance. The musical interplay can be used to support the infant in a quiet alert state, if appropriate for the infant. Vocal inflection may be used to promote eye opening, eye contact, and responses to social cues (e.g., smiling, cooing). The infant-directed improvised interaction will be paced and modified according to infant responses and engagement cues, and will be reversed or paused in response to disengagement cues. Conversely, for infants who have difficultly rousing for meal times, sessions can begin as described in "cautious use of sung/toned voice," with caregiver/therapist hand placed lightly and statically on infant's chest or back, or both hands/wrists lightly and statically cradling the sides of the infant and supporting the infant to align at midline. If the infant tolerates infant-directed singing in these positions, the caregiver/therapist can progress to include gentle rhythmic cues via light touch to coax the infant into a quiet alert state. If MT is used during breastfeeding attempts, rhythmic aspects of musical phrasing [52], and the addition of slightly stimulative vocal sounds can be matched to infant engagement/disengagement cues to support suck-swallow-breathe coordination and promote infant-parent co-regulation [53]. The music therapist may use simple acoustic instruments

(e.g., nylon string acoustic guitar, monochord) with single tones or simple accompaniment to accompany infant/caregiver during this phase, if the infant tolerates such additional stimulation without disengagement cues or physiological signs of overstimulation.

From 36 weeks PMA, MT will focus on expanded engagement in musical exchange. This phase applies when the infant demonstrates readiness to engage in increasingly more interactive levels of musical exchange. Caregivers interact musically with the infant, using vocal inflection and musical phrasing to encourage the infant to achieve a quiet, alert state and engage in eye contact, vocalization, and rudimentary social interaction, if appropriate for the infant. Depending upon infant readiness, caregivers may use their voices and physical positioning to promote auditory localization, auditory tracking, and eye contact; and their fingers and hands to promote reaching, grasping, and mouthing. The therapist will encourage the caregiver to adapt preferred lullabies and children's songs or to modify songs of kin [31, 43] in order to encourage musical dialogue with the infant, and the therapist may provide basic harmonic or melodic accompaniment as support.

Standard care during NICU: This will vary across countries, but will typically include necessary medical care and a limited amount of interventions to reduce stress among infants and to inform and promote safety in parents [54]. Components of standard care will be recorded at each site.

MT post-discharge from hospital: Infant-parent dyads will be offered 45-minute individual MT sessions, 7 times distributed across the first six months after discharge (2 times/month for the first month, and 1 time/month thereafter). These will occur at home or at municipal child health centers and comprise: (1) Verbal greeting and brief discussion of infant's progress (approx. 5 min). (2) Musical greeting of infant and caregiver, encouraging caregiver to participate (5 min). (3) Engagement in musical exchange following the procedures described in the "from 36 weeks" category above and incorporating adapted play songs, with therapist

modelling musical engagement (approx. 10 min). (4) Discussion of current infant/parent challenges and strategies for using musical interactions to address these needs, with therapist modelling musical techniques to promote self-regulation or to facilitate musical interaction, depending upon needs identified by the caregiver (approx. 10 min). (5) Caregiver demonstration of techniques discussed during session (approx. 10 min). (6) Musical closure and reminder of planned timing for next visit (approx. 5 min). Any siblings may be involved if desired by the caregiver, and sessions will incorporate musical instruments and resources present in the home, if appropriate for the infant. Subsequent sessions will follow a similar sequence, adjusted to infant developmental level and ongoing needs. The therapist will work in close dialogue with those providing standard aftercare procedures, when possible.

Standard care post-discharge from hospital: This includes follow-up visits and preventive interventions in primary or specialist health care as needed. Preventive interventions during the first year of life are focused on growth/eating/nourishment as well as psychomotor/sensory development and also include a focus on families and bonding [54]. Standard care may include other early intervention methods of care with the exception of other MT approaches.

Treatment guidelines for music therapy: MT during NICU and post-discharge phases will be conducted in accordance with a treatment guide established for this study. Guidelines will be grounded in current evidence-based practices, experiences from the Norwegian feasibility study, and feedback from our User Advisory Group and Scientific Advisory Committee. These treatment guidelines will be used in training the music therapists involved in the study, and will promote consistency of treatment implementation across study sites. The treatment guidelines will articulate guiding principles underlying the intervention, delineate the level of variation that is acceptable, and provide illustrative examples of approaches. Implementation of the guidelines will allow for individual tailoring to meet the needs of the infant and/or

parents, and presumes a music therapist trained specifically in the use of MT for premature infants and their families. The treatment guidelines will be available as a separate paper.

Assessment of treatment fidelity: In order to provide fidelity check measures as an estimate of treatment fidelity, music therapists will be asked to document the following after each MT session: approaches implemented, infant and parent responses, and any significant events or unusual circumstances. In addition to self-report fidelity checks, treatment fidelity will be evaluated by independent raters using video recordings to determine adherence to the method and competence in applying its approaches.

Outcomes

Unless indicated otherwise, all outcomes will be assessed at baseline; one to two days before discharge to home; at 6 months CA (end of MT; primary endpoint); and at 12 months of CA (Fig. 1, Fig. 2). All applicable outcomes (i.e. all that are scale-based) will be calculated as final values, but where baseline scores are available they will be included in the statistical models (see below). Data collectors and assessors will be trained in assessment procedures and blinded to participant allocation; success of blinding will be verified. For all self-report instruments we will use official translations, or if not available, we will translate according to recommended procedures with translations, back-translation and discussions before the final version is completed [55]. Psychometric properties of the instruments will be assessed across sites.

Primary outcome: Bonding between primary caregiver and infant at 6 months CA will be measured using the Postpartum Bonding Questionnaire (PBQ) [56, 57]; the same outcome will also be assessed at discharge and at 12 months CA. The PBQ is a parent-rated screening instrument for disorders of the early mother-infant relationship consisting of 25 statements on a six-point Likert scale (each 0-5; sum score ranging from 0 to 125; high = problematic), addressing problems in the mother-infant relationship based on weakened bonding; rejection

and anger; anxiety about care; and risk of abuse [58]. The scale is validated and widely used in clinical practice and research [39]. It has been translated and tested in several languages and cultures [57] and has been found to be reliable in mothers with or without depression or bonding problems [58]. Results from feasibility testing and user feedback in Norway confirmed the acceptability and relevance of the PBQ, also in comparison to alternative but less widespread measures that were considered. The scale covers both the more common and the rare but important problems that parents and infants can have.

Secondary infant outcomes will be as follows.

(1) The most important among the secondary outcomes is *child development* at 24 months of CA, as indicated by the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III). The Bayley-III is considered the gold standard for assessing development in young children up to 42 months [59]. At 24 months the tool is used routinely in many countries for extremely premature infants. Assessors will be trained and reliability-tested before conducting the assessments for this study, also in cases where the assessments are part of routine procedures, when possible. The three main composite scores of the Bayley-III are cognitive, language (receptive and expressive), and motor (fine and gross motor) development; each of the scales is standardized with a population mean of 100 (SD 15), with higher scores indicating better development. No total score covering all domains is available, but the most important areas for the present study will be language and cognition. The Bayley-III has US norms and has been used extensively for developmental assessments for premature infants (e.g. [60]).

(2) Infant development at 6 and 12 months CA will be assessed by the Ages and Stages Questionnaire, 3rd edition (ASQ-3) [45]. The ASQ-3 is an age-specific parent-reported screening questionnaire consisting of 30 items covering five developmental domains with five subscales: communication, fine-motor, gross-motor, problem-solving, and personal-social

(possible range 0 to 60) and a total score (possible range 0 to 300), with higher scores indicating better development.

(3) Infant socio-emotional development will be measured by the Ages and Stages Questionnaire Social-Emotional (ASQ:SE) at 6 and 12 months of CA. This is a parent-completed questionnaire with 19 or 22 Likert-scaled items (each 0-5-10), plus additional items for whether an item is of concern to the parent (each 0-5), resulting in a score ranging from 0-285 or 0-300, at 6 and 12 months respectively. Lower scores indicate better socio-emotional development [47, 48].

(4) Re-hospitalization during the first year of life (excluding outpatient visits), based on electronic health records or parent reports. This will be calculated as the time from initial discharge until first re-hospitalization.

Secondary parental outcomes include the following.

(1) Maternal depressive symptoms will be assessed with the Edinburgh Postnatal Depression Scale (EPDS) at baseline, 1-2 days prior to discharge, and at 6- and 12- months of infant CA. The 10-item validated self-report instrument assesses mothers' postpartum depressive symptoms, excluding somatic symptoms of depression that are common in new mothers (such as loss of energy, feeling tired, changes in appetite and sexual drive)[61]. Scores can range from 0 to 30, with high scores indicating more depressive symptoms.

(2) Level of anxiety (both mothers and fathers) will be assessed with the Generalized Anxiety Disorder Assessment (GAD-7) at baseline, 1-2 days prior to discharge, and at 6- and 12-months of infant CA. The self-report 7-item questionnaire serves as a screening tool and severity measure for generalized anxiety disorder [62]. Scores can range from 0 to 21, with higher scores indicating higher anxiety.

(3) Level of parental stress (both mothers and fathers) will be assessed with the Parental Stress Scale (PSS) at 6- and 12- months of infant CA. This is a self-report 18-item

questionnaire that assesses stress associated with parenting [63]. Scores can range from 18 to 90, with higher scores indicating higher stress.

Other measures: Specific *medical and social factors* relevant for subgroup analyses will include parents' socioeconomic status (collected at baseline) and infants' hearing status (collected at discharge). Additional open-ended questions will address other potential factors that might impact infant responsiveness (which may include e.g. intraventricular hemorrhage, metabolic disturbances, or genetic disorder among infants, and known mental health or substance use problems of parents). These will be drawn from hospital records and may be supplemented by parent self-reports.

Cost-effectiveness

We will explore and collect data necessary for analyzing cost-effectiveness both from a health services perspective (i.e. costs of all treatments incurred within the health sector including the costs of MT and standard care) and from the broader societal perspective (i.e. including all treatments incurred by the health sector and other indirect costs such as productivity losses and out-of-pocket expenses incurred by the parents). If clinical effectiveness is found, we will apply for separate funding to explore the additional cost to achieve a unit improvement in parent-infant bonding and explore the likelihood MT will be good value for money. This will be done through incremental cost-effectiveness ratios and willingness to pay analyses. Otherwise, these data will be used to describe the context in which the treatment took place.

Adverse events

All significant harms as well as unintended effects for each group will be collected and described by the site investigator, and reported to the core team. All adverse events that site investigators suspect may be related to MT and all serious adverse events will be reported to the Data and Safety Monitoring Committee by the core team. A special form to report trial-related adverse events will be developed and distributed.

Sample size and power calculation for the main comparison

No previous RCT examined effects of MT on the PBQ; two small RCTs [38] and a recent non-randomized study [46] examined mother-infant bonding, but provided insufficient data for meta-analysis. Studies using the PBQ with other interventions found effects ranging widely from around 0.25 to 9.0, with SDs ranging from 4 to 12 [11, 64, 65]. Assuming a difference of 4 points on the PBQ (SD = 8) as a minimal clinically important difference for this study, power of 80% will be achieved for each main effect (each tested on a two-sided 2.5% significance level, i.e. 5% with Bonferroni correction for two tests) with a sample size of 155. Taking into account some clustering by country (ICC 0.01; 5 countries), this is increased to 203. To allow for 20% attrition, we will aim to include 250 infants (approximately 50 in each country) and their parents. This sample size will also ensure power for testing proportion differences of about 15% (e.g. binary analysis of problematic bonding; re-hospitalization).

Special considerations are needed for multiple pregnancies (twins, triplets, etc.), which account for about 2% of all pregnancies in the Hordaland region of Norway [66], but are more commonly encountered in NICUs due to elevated risk of preterm birth. Although including all siblings would serve to increase the sample size, it may lower the resulting power due to cluster effects. Therefore, we will only formally enroll and analyze the first-born sibling of each multiple pregnancy, although all can receive the allocated intervention (see Eligibility criteria).

Recruitment

Recruitment at the first site is planned to commence in July 2018, and completion of recruitment is planned for the end of 2019. Enrollment will be completed in the NICU by a trained member of the unit staff according to the eligibility criteria. The staff person will be responsible for first contact with caregivers, providing an opportunity for informed consent.

We estimate that an 18-month period for recruitment will be sufficient to achieve the targeted sample size. Each site will aim to recruit approximately 50 infants and their parents; therefore, slow recruitment at some sites will be tolerable. Recruitment rates will be monitored carefully. Local and national partners responsible for primary care provision will serve as contact points after discharge and will be actively involved, wherever possible. Once an infant is randomized, the site investigator will make every reasonable effort to follow the infant and the parent/caregiver for the entire study period of 24 months. The site investigator will be responsible for developing local standard operating procedures for the site, in order to facilitate implementation of all aspects of the study. In addition, site investigators will develop post-recruitment retention strategies to promote retention (e.g., development of a newsletter directed to participants).

Randomization and allocation concealment

After site-specific informed consent and baseline assessment, participants will be randomly assigned to MT during NICU or standard care using a computer-generated randomization list, with ratio 1:1, in blocks with sizes of 2 or 4 varying randomly, stratified by site using email and an online system. The random allocation sequence will be generated and administered by people with no involvement in the clinical work to ensure allocation concealment. One potential issue with providing MT in shared NICU rooms is contamination. Parents may pick up strategies from other parents in the same room (or, likely to a lesser extent, from other parents or staff on the ward). We will assess contamination through the following questions at the end of each parent's participation in the study: "How often did you sing or play music with or for your child (daily/weekly/occasionally/never)? If so, in what way (please describe)? Did you learn from another parent in the NICU about using music (yes, please describe/no)?" Before discharge to home, participants will be randomized a second time to post-discharge MT or standard care in a 1:1 ratio, using the same procedures. This two-step randomization

was chosen as the best way to create balance among those remaining in the study for the post-discharge phase, and to avoid differential drop-out in the NICU phase due to expectations for the post-discharge phase. We will assess potential contamination in the post-discharge phase by asking participants if they engaged in MT with their infant outside of the study during the first year of the infant's life, and if so, the frequency and nature of such engagement.

Blinding

Due to the nature of the intervention neither participants nor staff can be blinded to allocation, but are reminded not to disclose the participant's allocation status to outcome assessors. All outcomes that are not self-reports will be conducted by an assessor blind to treatment allocation, and success of blinding will be tested by asking assessors.

Data analyses

Baseline analysis: Sociodemographic and clinical baseline properties for the groups will be characterized by descriptive methods (mean (SD), median [range], n (%)).

Primary analysis: We will use an intention-to-treat (ITT) approach using all available data from all participants as randomized, regardless of the intervention actually received. Multiple imputation will be used for missing data, if applicable [67].

Effects will be examined by testing the randomized groups for differences in the primary endpoint (t-test or Mann-Whitney; change in PBQ scores to 6 months CA), as well as by fitting linear mixed models. In the first modeling step we will assess the effect of the first randomization (Fig. 1) using the following model:

$$PBQ_{it} = \beta_0 + \beta_1\, time_t + \beta_2\, gr_i + \beta_{12}\, time_t\, gr_i + U_i + \varepsilon_{it} \ ,$$

where PBQ_{it} denotes the PBQ score for participant i at measurement t, $time_t$ the time from baseline at measurement t and gr_i the randomization group of participant i. β_0, β_1, β_2 and β_{12} are the coefficients estimated in the model, U_i is an individual random term per participant

and ε_{it} an independent, identically distributed error term. In the second step we refine the model to take into account both randomization steps, leading to the extended model:

$PBQ_{it} = \beta_0 + \beta_1 time_t + \beta_2 grR1_i + \beta_{12} time_t grR1_i + \beta_3 grR2_i + \beta_{13} time_t grR2_i + U + \varepsilon_{it}$,

with the same notation as above and $grR1_i$ and $grR2i$ denoting the groups from the first and second randomization, respectively. In these models β_1 describes a group-independent time effect, β_2 and β_3 a time-independent group effect, and β_{12} and β_{13} the time-dependent change of the group effect. We will investigate both linear and simple contrasts (comparing each time point with the baseline) in time to assess the treatment effect.

Secondary analyses: The same analyses will be done for the secondary outcomes; using an analogous generalized linear mixed model for binary outcomes. Per-protocol analyses will include those who received at least 6 MT sessions in the NICU and at least 5 MT sessions post-discharge, respectively; these are considered the minimum numbers for the intervention to be successful.

Subgroup analyses: Additionally, we will conduct exploratory statistical analyses for pre-specified subgroups (sex; GA at birth [<28 wks, 28 to <32 wks, 32 to < 35wks]; hearing status at discharge [normal vs. abnormal]; bonding at baseline [PBQ impaired bonding score ≥ 11 vs. <11]; parental socioeconomic status [poor vs. other] [68] as well as qualitative/mixed-methods analyses of process data to maximize learning.

Data management and collection methods

In order to maintain participant confidentiality all information will be stored with ID code numbers. The ID code numbers will be unrelated to participants' identifiers, except in a central file with the participants' contact details. All data will be stored on an electronic database management system located on a secure server with password-controlled access provided for research data collectors.

To ensure data quality, a trial database will be set up and maintained using a safe server (Uni Research Health Data Storage, UHEADS) and OpenClinica software. UHEADS is a system for safely storing health research data that accommodates the safe upload, storage and retrieval of any sensitive research data. OpenClinica is a web-based system for electronic data capture and clinical data management for multicenter clinical trials, which conforms to relevant international standards for health research. Uni Research AS runs an open source version of OpenClinica. A manual for using OpenClinica in this study will be created and distributed to collaborators. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records identified by the ID code number. All study-related information on paper, including questionnaires, and administrative forms will be securely stored in locked file cabinets in areas with limited access. After publication, de-identified individual participant data of the main variables will be stored on a publicly available repository to ensure replicability and transparency.

Monitoring

The site investigators will practice entering data so that the core team can confirm that site investigators are proficient in all aspects of data entry, query response, and communication with the team at each site. Uploaded data will be regularly checked by a core team researcher (Ł.B.) in order to ensure good quality data. Monitoring will follow a risk-based approach, with site investigators and central team members sharing the responsibility for quality and completeness of data. Core team members will conduct monitoring of source documents via scan of randomly chosen questionnaires at all enrolling LongSTEP sites, and will conduct on-site monitoring visits as needed. Through these on-site visits we will audit the overall quality and completeness of the data, examine source documents and interview coordinators to determine whether data reported in OpenClinica are complete and accurate, and whether the

clinical site has complied with the requirements of the protocol. If a problem is identified, the core team will assist the site investigator in resolving the issues.

Oversight, auditing, and advisory committees

Data and Safety Monitoring Committee (DSMC): An independent panel of three clinicians and methodologists with relevant expertise but no direct involvement in the trial has been established to ensure research integrity and safety of participants in the trial. After an initial protocol review meeting, the DSMC will check the general progress of the clinical trial including recruitment and completeness of follow-up; safety; and any other unforeseen events. To this end, the DSMC will receive updated reports from the project statistician, which may be unblinded with respect to intervention arms. Other project team members will not have access to such unblinded reports and will not attend the closed part of the DSMC meetings where such content is discussed. No interim efficacy analysis is planned for this trial.

Trial Steering Committee (TSC): The TSC will consist of one representative from each recruiting site, two user representatives, and two representatives from the core team. It will monitor trial progress, will receive recommendations from the DSMC, and will be involved in all decisions about protocol amendments or other changes in the trial.

User Advisory Group (UAG): An advisory group consisting of parents of premature infants in Norway has been established for this study. This group will be important for eliciting user feedback and ensuring relevance of the study, including any protocol amendments, as well as helping to ensure efficient recruitment and dissemination strategies. Similar involvement of users in other countries will be encouraged.

Scientific Advisory Committee (SAC): An international group of clinicians and researchers with relevant clinical expertise was established during project development and will continue

to advise on various aspects related to development and implementation of the study. The panel includes experts in areas such as MT, neonatology, and psychology.

Research ethics approval

The protocol, informed consent forms, and other requested documents will be reviewed and approved by the relevant ethical review bodies in each country. Ethical approval will be secured before the start of recruitment at each site. Any modifications to the protocol which may impact on the potential benefit or safety of participants will also be agreed upon by the ethics committee at each site prior to implementation in accordance with local regulations. Site-specific written informed consent will be obtained postnatally following routine practices in the NICU. A trained staff of the trial will inform parents/caregivers about the study and provide an opportunity for informed consent. The parent/caregiver will receive written and oral explanation of the proposed research project, including information regarding the research project, the aims of the project, the duration of the participant's involvement, the expected benefits to the participant and others, the nature of the intervention, and the procedures involved in participation. It will be emphasized that enrolment in the study is voluntary, that parents/caregivers can withdraw at any time from all or part of the study, and that any decision they take in this respect will have no bearing on the medical care received. Additionally, it we be highlighted that information generated by the study will be published, but that no details will be divulged from which the participant could be identified. Primary caregivers will be informed of whom to contact in an emergency, and the staff will be available to answer questions.

Dissemination

Dissemination of the findings will apply to local, national, and international levels. Aspects related to the feasibility of implementing MT in the hospital and in primary care and region-specific and culture-specific aspects of treatment implementation will be submitted to

corresponding specialized interdisciplinary journals. Main results of the trial concerning clinical effectiveness will be submitted to a leading medical journal. Additional results of exploratory statistical analyses and qualitative/mixed-methods analyses of process data will be published in specialized international journals. Beyond journal publications, we will disseminate results through presentations at national and international conferences. Popular dissemination, particularly to users, their families, user organizations, health services, and the general public will be achieved via a periodic newsletter, educational brochures and/or popular press articles.

Discussion

Controlled research on the impact of MT for premature infants and their caregivers demonstrates short-term improvements in infant physiologic and behavior states, feeding behavior, and length of hospital stay, as well as decreases in parental distress and anxiety [31, 34, 38]. LongSTEP fills a critical gap in knowledge by providing MT over a longer term from hospitalization through the first six months of life, and by assessing long-term outcomes of MT for both infant and parents during the first two years of the infant's life.

Since MT for premature infants and their caregivers is an emerging area of practice and research within Scandinavia, this study aims to integrate best available evidence from international developments with standards of practice existing in specific national health care environments, to create a model of care that is culturally-relevant for social support societies. LongSTEP consists of MT with a high level of parental engagement during the course of NICU hospitalization and a support- and consult-to-parent model of MT for the first six months following discharge. The model enables parents to assume a central role in the care of their infant, with the music therapist providing support and coaching to help parents to use their innate resources to promote developmentally-appropriate co-regulation of the

parent/infant dyad, improve quality of interaction and enable healthy bonding during this vulnerable time. The long-term aim is to assure healthy infant-parent relation and improve child developmental outcomes and promote parental psychological well-being over the first two years of the infant's life.

The pragmatic nature of this trial and its high clinical applicability are reflected in several dimensions, as described in the pragmatic-explanatory continuum indicator summary (PRECIS) [69]. Eligibility criteria are designed to be as inclusive as possible to promote applicability of the evidence with respect to a broad population. Broad inclusion criteria ensure enrolment of participants with heterogeneous characteristics similar to those seen by clinicians in daily practice, and exclusion criteria are narrow and exist only to ensure infant safety. Another pragmatic dimension of this trial is flexible MT delivered by a qualified music therapist. MT is tailored to infants over a broad range of PMA and also incorporates family and cultural preferences. Additionally, we do not restrict if or how co-interventions will be delivered. Participants in all arms will receive standard care. Analysis of primary outcome will include all individuals regardless of compliance in order to test if the intervention works under usual conditions, with all the noise inherent therein.

As a limitation it should be noted that clinical benefits as well as resulting societal benefits related to disability prevention and economic outcomes are likely to occur over a longer term. To address this, we will also include the possibility in the consent forms to collect later follow-up data, but these will be beyond the present project. In summary, this pragmatic trial will determine the effects of MT under usual conditions, and the design as a multicenter trial will further ensure wide generalizability.

The project's social impact includes filling gaps in knowledge regarding the long-term impact of MT with preterm infants/caregivers, including highly user-relevant outcomes. The high applicability of this trial will facilitate ongoing development of evidence-based care for

preterm infants. Opportunities for improved training of music therapists and effective implementation of MT in neonatal care will apply both to countries where MT in this area is new and to countries that already have a more established foundation. Specifically, LongSTEP will make a unique contribution to continuity of care by bridging intervention from NICU hospitalization to municipal and home settings post-discharge. In addition, LongSTEP fosters interdisciplinary collaboration between specialist and primary/municipal health care services (psychologists, nurses, physicians, music therapists).

In conclusion, LongSTEP builds off of evidence-based practice in neonatal MT, which supports the use of infant-specific MT tailored to developmental level and provided in conjunction with primary caregivers. The project will advance previous knowledge by suggesting a pathway by which MT can promote infant development while also improving parental psychological outcomes. Coaching parents in the use of music may help improve infant regulation and decrease parental stress during parent/infant interactions, which in turn may promote bonding and contribute to better infant developmental and parental psychological outcomes.

Abbreviations
ASQ-3 – Ages and Stages Questionnaire (3rd edition); ASQ:SE – Ages and Stages Questionnaire: Social-Emotional; PBQ – Postpartum Bonding Questionnaire; Bayley-III – Bayley Scales of Infant and Toddler Development (3rd edition); EPDS – Edinburgh Postnatal Depression Scale; CA – corrected age; GA – gestational age; GAD-7 – Generalized Anxiety Disorder Assessment; MT – music therapy; NICU – neonatal intensive care unit; PMA - postmenstrual age; PSS – Parental Stress Scale; RCT - randomized controlled trial.

Ethics approval and consent to participate
The Regional Committees for Medical and Health Research Ethics (2018/994/REK Nord, date of approval: 03 July 2018) approved of the main study. A protocol for feasibility trials in Norway and Poland was approved by the Regional Committees for Medical and Health Research Ethics (2017/2249/REK Nord, date of approval: 05 December 2017) and the Research Ethics Board at the University of Gdańsk (no 3/2018, date of approval: 12 April 2018), respectively.

Consent for publication – Not applicable.

Availability of data and material – Not applicable.

Competing interests
ME, TG, CGh, and CGo are clinically trained music therapists. The other authors declare that they have no competing interests.

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Table 1. Key elements of the music therapy intervention

Phase of intervention	Key elements	Intervention description
All phases	High parental/caregiver involvement and resource-oriented	Parents/caregivers are recognized as possessing inherent resources that can aid their infant and themselves following premature birth. In all aspects of the MT intervention, parents are encouraged to take a leading role, while receiving support from the music therapist.
	Therapeutic benefit aimed at infant-parent dyad/triad	MT promotes infant-parent co-regulation and includes psychotherapeutic support of parents.
	Neurodevelopmentally appropriate	Specific use of MT is matched to infant PMA, familial/cultural preferences, and infant's readiness.
	Positioning to promote beneficial co-regulation	Infant/parent positioning is considered a vital component for promoting beneficial self-regulation.
	Based on needs of infant/parent(s) in the moment	Infant and family needs are assessed at the beginning of each intervention phase (during NICU and post-discharge), and during each MT session to assure that use of MT matches needs in the moment (e.g. promoting sleep vs. encouraging quiet alert interaction).
	Parental voice as foundation for infant-directed use of song	Parents' use of their sung (and when necessary, spoken) voice along with positioning and physical presence forms the foundation of an attuned response to their infant. Parents' sung voice, facial expressions and vocal expressions vary in response to infant's engagement/disengagement cues, breathing rate, gesticulations and facial expressions, so that the music

		remains infant-directed.
Infant medically stable, in NICU, 26 to below 32 wks PMA	Cautious use of sung/toned voice	Predominantly wordless singing voice is matched to infant breathing patterns, facial expressions and movements, and either promotes sleep or a quiet alert state depending upon infant's needs.
	Incorporation of familiar songs adapted for the premature neonate	Parents learn how to adapt songs that are familiar/preferred so that they are appropriate for the preterm neonate (e.g. simplified and/or transformed into lullaby style).
Infant medically stable, in NICU, 32 wks to below 36 wks PMA†	Cautious use of infant-directed song with expanded sensory experience	Culturally-relevant, caregiver-preferred songs are adapted in the moment to match infant breathing rate, engagement/disengagement cues, facial expressions and gesticulations, to promote musical interplay when appropriate for the infant. The musical interplay may include dynamic touch, and parents' use of vocal inflection and phrasing to promote rudimentary musical dialogue, eye contact and social responses.
	Addition of rhythmic cues and musical phrasing cues to support feeding attempts	By adapting familiar songs, rhythmic aspects of musical phrasing, and the addition of mildly stimulative vocal sounds can be matched to infant engagement/disengagement cues to support suck-swallow-breathe coordination and promote co-regulation.
	Accompanying instruments are used to support the dyad/triad, with complexity matched to infant readiness	The music therapist may use acoustic instruments (e.g. nylon string acoustic guitar, monochord) to provide single tones or simple accompaniment to support infant/parent, if infant tolerates the added musical stimuli well.

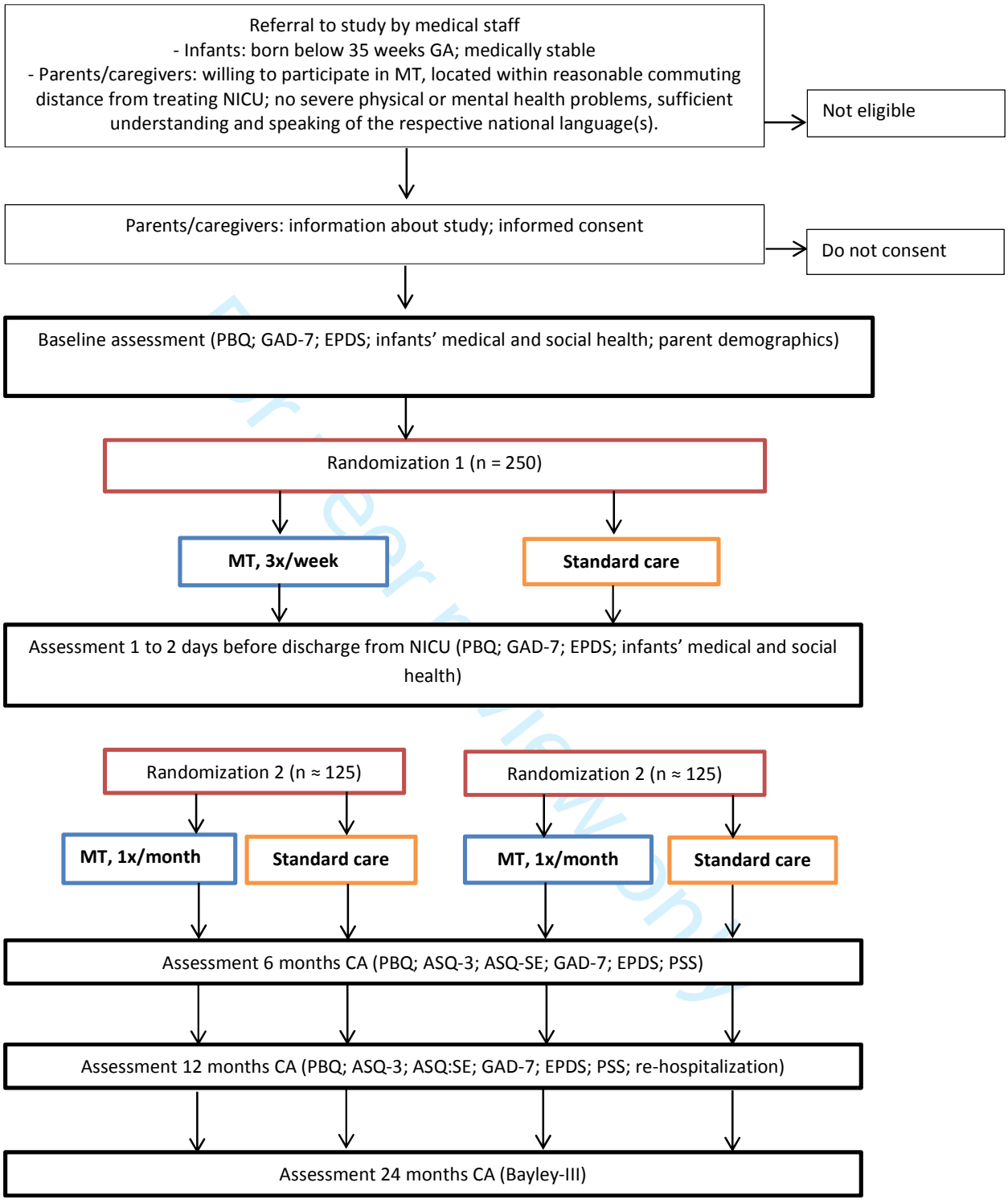
Infant medically stable, in NICU, from 36 wks PMA	Expanded engagement in musical exchange	Parents adapt preferred songs so that vocal inflection and musical phrasing reflect infant responses and promote eye contact, vocalization and rudimentary social interaction, if appropriate for the infant. Parents may also use their positioning while singing to promote auditory localization, auditory tracking or eye contact.
Post-discharge from NICU	Based on needs of infant/parent(s) in the moment and in relation to recent challenges	Infant and family needs are assessed at the beginning of each MT session, and particular strengths and challenges that have arisen in the past 2 weeks are identified and targeted (e.g. transitioning between behavior states, maintaining alertness during feeding, experiencing rewarding relation).
	Expanded engagement in musical exchange, including adapted play songs, when appropriate	Parents engage in and expand upon musical approaches from the previous phase, matched to infant/family needs, and music therapist models variations and adaptations as needed.
	Identification of musical resources that may help address current challenges or build upon current strengths	Parents and music therapist brainstorm how music can be adapted and used for infant/family needs, and parents have a chance to try out certain approaches with support, if appropriate.

† Elements of the prior phase apply to subsequent phases. An infant remains in the previous phase (despite PMA) until ready to receive more expanded stimulation. The combination of elements used within each phase will depend upon the infant's needs in the moment.

Figure captions

Figure 1. Flow of participants though the study: Illustration of the study design
Note. ASQ-3 – Ages and Stages Questionnaire (3rd edition); ASQ:SE – Ages and Stages Questionnaire: Social-Emotional; Bayley-III – Bayley Scales of Infant and Toddler Development (3rd edition); CA – corrected age (chronological age reduced by number of weeks born preterm); EPDS – Edinburgh Postnatal Depression Scale; GAD-7 – Generalized Anxiety Disorder Assessment; PBQ – Postpartum Bonding Questionnaire; PSS – Parental Stress Scale.

Figure 2. Schedule of enrolment, interventions, and assessments
Abbreviations: ASQ-3 – Ages and Stages Questionnaire (3rd edition); ASQ:SE – Ages and Stages Questionnaire: Social-Emotional; Bayley-III – Bayley Scales of Infant and Toddler Development (3rd edition); CA – corrected age (chronological age reduced by number of weeks born preterm); EPDS – Edinburgh Postnatal Depression Scale; GAD-7 – Generalized Anxiety Disorder Assessment; PBQ – Postpartum Bonding Questionnaire; PSS – Parental Stress Scale.



	STUDY PERIOD						
	Enrol-ment	**1st random-ization**	**Post 1st allocation**	**2nd random-ization**	**Post 2nd allocation**		
TIMEPOINT	***before random-ization***	**0**	***during NICU stay***	***at discharge from NICU***	***6 months CA***	***12 months CA***	***24 months CA***
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X		X			
INTERVENTIONS:							
MT		←	—	←	—		
Standard care		←	—	—	—	—	→
ASSESSMENTS:							
parent demographics	X						
PBQ; GAD-7; EPDS	X		X		X	X	
ASQ-3; ASQ:SE; PSS					X	X	
Bayley-III							X
Re-hospitalization				←	—	—	
Adverse events		←	—	—	—	—	

SPIRIT 2013 Checklist for the LongSTEP project: 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	n/a
Funding	4	Sources and types of financial, material, and other support	32
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	1
	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	2; 32
	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)	27-28

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	5-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
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)	11-12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-17; Table 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)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17-18
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16-17
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	18-21
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)	10; Fig. 1; Fig. 2

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	21-22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	22-23
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	23
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	23-24
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	23-24
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	24
	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	18; 25-26
	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	23

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	25-26
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	24-25
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	25
	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)	24-25
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	26-27
	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	27
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; 26-27
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	26-27
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10-11; 27-28; 32
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)	27

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21-22; 27-28
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	25-26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32
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	n/a
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	28-29
	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	26
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on 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.

BMJ Open

Longitudinal Study of music Therapy's Effectiveness for Premature infants and their caregivers (LongSTEP): protocol for an international randomized trial

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Complete List of Authors:	Ghetti, Claire; University of Bergen, GAMUT - The Grieg Academy Music Therapy Research Centre, The Grieg Academy - Dept. of Music; NORCE Norwegian Research Centre AS Bieleninik, Łucja; Uniwersytet Gdanski, Institute of Psychology; NORCE Norwegian Research Centre AS Hysing, Mari; University of Bergen, Department of Psychosocial Science; NORCE Norwegian Research Centre AS, Regional Center for Child and Youth Mental Health and Child Welfare Kvestad, Ingrid; NORCE Norwegian Research Centre AS, Regional Center for Child and Youth Mental Health and Child Welfare Assmus, Jörg; NORCE Norwegian Research Centre AS, GAMUT - The Grieg Academy Music Therapy Research Centre Romeo, Renee; King's College London, King's Health Economics Ettenberger, Mark; Hospital Universitario de la Fundacion Santa Fe de Bogota; SONO - Centro de Musicoterapia Arnon, Shmuel; Meir Medical Center, Neonatal Department; Tel Aviv University, Sackler School of Medicine Vederhus, Bente; Haukeland University Hospital, Department of Pediatrics Söderström Gaden, Tora; NORCE Norwegian Research Centre AS, GAMUT - The Grieg Academy Music Therapy Research Centre Gold, Christian; NORCE Norwegian Research Centre AS, GAMUT - The Grieg Academy Music Therapy Research Centre
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Longitudinal Study of music Therapy's Effectiveness for Premature infants and their caregivers (LongSTEP): protocol for an international randomized trial

Authors: Claire Ghetti†*, Łucja Bieleninik†, Mari Hysing, Ingrid Kvestad, Jörg Assmus, Renee Romeo, Mark Ettenberger, Shmuel Arnon, Bente Johanne Vederhus, Tora Söderström Gaden, Christian Gold†
†Equal contributors

***corresponding author**

Affiliations:
*Claire Ghetti, PhD, GAMUT – The Grieg Academy Music Therapy Research Centre, The Grieg Academy – Dept. of Music, University of Bergen, Postbox 7805, 5020 Bergen, Norway; GAMUT, NORCE Norwegian Research Centre AS, Bergen, Norway; Email: claire.ghetti@uib.no. Phone: +47 465 08 095

Łucja Bieleninik, PhD, Institute of Psychology, University of Gdańsk, Bażyńskiego 4, 80-309 Gdańsk, Poland; GAMUT – The Grieg Academy Music Therapy Research Centre, NORCE Norwegian Research Centre AS, Postbox 7805, 5020 Bergen, Norway; Email: lubi@norceresearch.no

Mari Hysing, PhD, PsyD, Department of Psychosocial Science, University of Bergen, Postbox 7807, 5020 Bergen, Norway; Regional Center for Child and Youth Mental Health and Child Welfare, NORCE Norwegian Research Centre AS, Postbox 7810, 5020 Bergen, Norway; Email: mari.hysing@uib.no

Ingrid Kvestad, PhD, PsyD, Regional Center for Child and Youth Mental Health and Child Welfare, NORCE Norwegian Research Centre AS, Postbox 7810, 5020 Bergen, Norway; Email: inkv@norceresearch.no

Jörg Assmus, PhD, GAMUT – The Grieg Academy Music Therapy Research Centre, NORCE Norwegian Research Centre AS, Postbox 7805, 5020 Bergen, Norway; Email: jras@norceresearch.no

Renee Romeo, PhD, King's Health Economics, King's College London, Decrespigny Park, London, SE5 8AF, United Kingdom; Email: renee.romeo@kcl.ac.uk

Mark Ettenberger, PhD, University Hospital Fundación Santa Fe de Bogotá, Colombia; SONO – Centro de Musicoterapia, Bogotá, Colombia; Email: mark.ettenberger@sono.la

Shmuel Arnon, MD, Neonatal Department, Meir Medical Center, Kfar-Saba, 44281, Israel; Sackler School of Medicine, Tel-Aviv University, Israel; Email: harnon@netvision.net.il

Bente Johanne Vederhus, PhD, RN, Haukeland University Hospital, Department of Pediatrics, Postbox 1400, 5021 Bergen, Norway; Email: bente.vederhus@helse-bergen.no

Tora Söderström Gaden, GAMUT – The Grieg Academy Music Therapy Research Centre, NORCE Norwegian Research Centre AS, Postbox 7805, 5020 Bergen, Norway. Email: toga@norceresearch.no

Christian Gold, PhD, GAMUT – The Grieg Academy Music Therapy Research Centre, NORCE Norwegian Research Centre AS, Postbox 7805, 5020 Bergen, Norway. Email: christian.gold@norceresearch.no

Authors' contributions:
ŁB, CGh and CGo conceived the study, developed the study design, and drafted the manuscript. JA developed the study design, provided statistical expertise in clinical trial design and is conducting the primary statistical analysis. IK, MH, RR, ME, SA, BV and TG contributed to the study design, with IK and MH contributing in particular the definition of outcomes. All authors contributed to refinement of the study protocol and approved the final manuscript.

Abstract

Introduction: Preterm birth has major medical, psychological and socio-economic consequences worldwide. Music therapy (MT) has positive effects on physiological measures of preterm infants and maternal anxiety, but rigorous studies including long-term follow-up are missing. Drawing upon caregivers' inherent resources, this study emphasizes caregiver involvement in MT to promote attuned, developmentally-appropriate musical interactions that may be of mutual benefit to infant and parent. This study will determine whether MT, as delivered by a qualified music therapist during neonatal intensive care unit (NICU) hospitalization and/or in home/municipal settings following discharge, is superior to standard care in improving bonding between primary caregivers and preterm infants, parent well-being and infant development.

Methods and analysis: *Design:* International multi-center, assessor-blind, 2x2 factorial, pragmatic randomized controlled trial; informed by a completed feasibility study. *Participants:* 250 preterm infants and their parents. *Intervention:* MT focusing on parental singing specifically tailored to infant responses, will be delivered during NICU and/or during a post-discharge 6-month period. *Primary outcome:* Changes in mother-infant bonding at 6 months corrected age (CA), as measured by the Postpartum Bonding Questionnaire. *Secondary outcomes*: Mother-infant bonding at discharge and at 12 months CA; child development over 24 months; and parental depression, anxiety, and stress, and infant re-hospitalization, all over 12 months.

Ethics and dissemination: The Regional Committees for Medical and Health Research Ethics approved the study (2018/994/REK Nord, 03 July 2018). Service users were involved in development of the study and will be involved in implementation and dissemination. Dissemination of findings will apply to local, national, and international levels.

Trial registration: Registered at ClinicalTrials.gov, registration number NCT03564184. Will be registered at HelseNorge by participating Norwegian hospitals.

Keywords: prematurity, caregiver, bonding**,** music therapy, non-pharmacological interventions, psychosocial interventions, randomized controlled trial

Strengths and limitations of this study

- Following several studies suggesting short-term effects of MT for premature infants, this study will examine longer-term effects up to two years.
- Parents will be actively included in MT, with the aim of improving outcomes of both infants and parents.
- MT will be continued after discharge from hospital, thus providing a bridge between specialized and primary health care.
- As a multinational trial, results will be relevant across a range of settings in diverse societies that enable social support from families.
- Due to the nature of the intervention, participants cannot be blinded. Similarly, most outcomes cannot be blinded because they rely on parent reports.

Background

The global average rate of preterm birth is around 11% worldwide corresponding to 15 million preterm infants each year [1, 2]. Over one million die as a direct result of prematurity, and another million show lifetime impairments [3]. With improved survival rates, there is growing concern for long lasting complications including mental health problems, cognitive impairments, and poorer quality of life [1, 4-6]. Moreover, the economic burden of preterm birth includes increased cost of neonatal care, long-term costs associated with complex health status, and losses in economic productivity over the lifespan [7].

Premature labor is perceived as a stressful [8] and traumatic [9, 10] event that can interrupt mothers' antenatal bonding [11]. Families of premature infants can experience higher levels of stress, anxiety, and fear for the infant's safety, as well as insecurity and powerlessness [10, 12]. Mothers are at risk for postpartum depression, posttraumatic stress disorder, feelings of guilt, mourning, and lack of self-worth [13]. Fathers experience significant stress, which may extend beyond the acute phase following the infant's birth [14]. Supportive and educational interventions provided to fathers in the acute phase of the infant's hospitalization can empower their fathering ability and reduce paternal stress [15].

Separation due to NICU stay and prolonged hospitalization may complicate the development of healthy parent-infant bonding and in some cases adversely impact the formation of secure attachment [10, 16]. Mother-infant relationship plays a central role in the child's socio-emotional development and formation of future intimate relationships [17, 18]. Mothers' psychological well-being [19] or postpartum depression [20] are important factors affecting parent-infant relationship in the postnatal period. However, even with sensitive parenting, children born very preterm or very low birthweight are at higher risk of demonstrating disorganized attachment than those born full-term, and neurological impairment predicts this disorganized attachment [21]. Involving fathers in infant care,

including skin-to-skin care, during the first days of the infant's life can positively impact the bonding process while improving support to partners [22], and can lead to improved self-esteem, feelings of closeness to the infant, and perception of more equal parenthood [23]. Decreasing maternal stress and reducing early separation during NICU hospitalization may be beneficial for long-term outcomes [24].

MT is part of NICU standard treatment in some hospitals in several countries, but supply is usually limited even where that is the case. MT in infant critical care involves the informed use of music and a therapeutic relationship to promote infant development and facilitate bonding with primary caregivers [25]. MT promotes infant sensory regulation and may contribute to neurological development [26, 27]. Incorporating parents as active partners in implementing MT during the NICU stay leads to decreased infant and parent distress [28], and may thus promote bonding [29]. MT beneficially impacts infant physiological parameters, behavior state, weight gain and feeding ability, and may reduce hospital stay [26, 30-34]. There are also some indications of a positive impact of music on sleep for premature infants [31, 35, 36]. MT provides a culturally-sensitive form of family-centered care that empowers both mothers and fathers in the care of their premature infants [29]. MT-based consult-to-parent models, such as the *Time Together* adaptation of contingent singing into a parent education program, can help extend benefits to families beyond those most prioritized to receive MT services [37].

In a rigorous systematic review and meta-analysis of randomized controlled trials (RCTs), a large and favorable effect of MT on respiratory rate and maternal anxiety was confirmed [38]; however, several areas require further investigation. Rigorously designed and adequately powered studies using standardized outcome measures and interventions implemented by music therapists with specialized NICU training are required. Parallel RCTs to evaluate long-term effects of MT, and extending intervention periods past discharge from NICU, are

required to assess long-term impact, which is a substantial gap in present knowledge [38]. Studies examining longitudinal provision of MT tailored to different stages of infant development [28] and long-term effects of MT on the development of healthy parent-infant bonding and secure attachment are needed [26, 38].

Building on promising results from phase II studies and meta-analyses, LongSTEP is the first phase III trial worldwide of MT's effectiveness for premature infants and their caregivers. This trial will determine whether MT as delivered by a qualified music therapist during NICU hospitalization and/or after discharge to home is superior to standard care in improving bonding between primary caregivers and preterm infants. This project promotes continuity of care by bridging the transition from hospital to home and uses family-centered developmental care. Conducting the study in several countries with high levels of parental presence in the NICU, provides sufficient sample size to analyze treatment effects. The results will inform the effective use of music therapy across levels of health care for the participating NICUs in Europe, the Middle East, and South America. This study will contribute to an improved understanding of the relation between music and health and will enable evidence-based recommendations for the application of MT in primary health care services.

Objectives

The primary objective of this study is to evaluate the effect of MT on parent-infant bonding at 6 months CA.

Secondary objectives are as follows:

- To examine effects of MT on premature infants' general and socio-emotional development.
- To examine effects of MT on parents' symptoms of depression, anxiety, and stress.

- To examine medical and social factors of premature infants (sex, GA at birth, hearing status) and their parents (bonding, socioeconomic status, breastfeeding, skin-to-skin care) that may be associated with effects of MT.
- To prepare for examining cost-effectiveness and longer-term evaluation of effects.

We hypothesize that MT during or after NICU, compared to standard care alone, will lead to better parent-infant bonding, which in turn may beneficially impact infant development and parent mental health outcomes. Effects of MT may depend on medical and social factors. Clinical effectiveness may be associated with cost-effectiveness and may be sustained in the longer term.

Methods

Design

The Longitudinal Study of music Therapy's Effectiveness for Premature infants and their caregivers (LongSTEP) is designed as a 2x2 factorial, international, multi-center, assessor-blind pragmatic RCT to evaluate the long-term effect of MT in NICU and/or after discharge on premature infants and their primary caregivers across a 12-month time period (Fig. 1). The factorial design entails a two-phase protocol covering both the stay in the NICU and follow-up care after discharge from hospital, with two randomization time points, and tests the independent effect of each combination: NICU-MT, post-discharge MT, both, or neither, as well as interactions between them.

Patient and public involvement

Parents of premature infants, hereafter referred to as "users," play an important role in various aspects of this study. We consulted with users during original development of the project proposal to assure that our research question is highly pertinent to parents of premature infants, to estimate level of burden of the intervention, and to assess if the intervention is

likely to result in benefits that would be of value to users. We incorporated feedback from users in protocol development, both before and after securing funding. We developed a user advisory group to advise us on selection of outcome measures, feasibility of study design and intervention implementation, and this group will continue to serve an important role during the implementation of the study as described in the section on advisory committees. We will disseminate results of the study to users via popular publications, presentations to parent organizations, and informational pamphlets with recommendations for evidence-based practices.

Pilot testing and user feedback

A feasibility study was conducted at one Norwegian NICU (initiated January 2018) to determine acceptability and suitability of the intervention and study procedures and to obtain parental perspectives in order to inform design of the main study. Pilot testing evaluated feasibility in the areas of participant recruitment, delivery of study conditions, planned assessments, and retention, as well as tracking of treatment occurring as part of standard care. Following ethics approval, three families at a Norwegian NICU were offered MT 2 times/week during NICU hospitalization and 2 times/month during the first 3 months after discharge home. Follow-up interviews with parents revealed that parents were willing to take part in MT in the NICU and sing for their infants, and that MT offered a break from typical hospital routines and a different way of "reading" and relating to their infants. Parents found the self-report outcome measures acceptable and the nature of participation in MT as well as the frequency of sessions feasible and comfortable. Parents stated they would also have been willing to participate in the study if designed as an RCT despite the chance of being allocated to standard care.

A primary aim of the feasibility study was to determine whether the Postpartum Bonding Questionnaire (PBQ) should be retained as a primary outcome in the subsequent main trial.

The PBQ is validated and widely used in the literature [39], but we wished to explore its acceptability and perceived relevance with mothers in the feasibility study. While the full results will be published separately, preliminary analysis from the Norwegian feasibility study revealed that the PBQ scored on relevant items, changed over time, and mothers expressed no particular objections to completing its items. Results from the feasibility study and discussion with parents in our User Advisory Group informed our decision to retain the PBQ as a primary outcome measure for the main study.

The feasibility study also enabled us to test logistical parameters related to post-discharge MT. We provided post-discharge sessions in the home setting, following advice from our User Advisory Group. Based on the results from feasibility testing, we decided to adopt the following frequency in the main study to make consistency of sessions more feasible: 2 times during the first month following discharge from the NICU, and 1 time per month thereafter for a total period of 6 months.

Trial procedures

After informed consent and baseline assessment, participants will be randomly assigned to receive either MT plus standard care or standard care alone during their stay at the NICU. The intervention period will start immediately following randomization and will last until the infant's initial discharge from hospital. Participants will be asked to complete the discharge assessments one to two days before discharge to home; for those who are unable to complete them before discharge, assessments will be valid if completed up to one week after discharge. Upon completion of discharge assessments, participants will be randomly allocated to receive either post-discharge MT in home or municipal settings along with standard primary care, or standard primary care alone across a 6-month time period. Standard care may include other early intervention methods of care with the exception of other MT approaches. Participants are free to attend any type of treatment or therapeutic interventions in a post-partum setting,

but they will be asked not to attend MT outside the study context through 12 months corrected age (CA; defined as chronological age reduced by number of weeks born before 40 weeks of gestation [40]). This time frame is sufficient because the hypotheses of the study concern the effects of early MT during NICU or post-discharge; however, the receipt of any MT during the first 24 months CA outside the study will be recorded. Outcomes will be assessed at several time points: at baseline; one to two days before discharge to home (end of MT during NICU); at 6 months CA (end of post-discharge MT; primary endpoint); 12 and 24 months CA (Fig. 1, 2). Treatment fidelity (adherence) will be evaluated by independent raters using audio and video recordings as described further below. The study has been designed in accordance with the SPIRIT 2013 statement (see Additional file 1 for complete checklist). Ethical approval for the study has been granted by The Regional Committees for Medical and Health Research Ethics (2018/994/REK Nord) and supplemental ethical approval from each participating country was secured from relevant ethics committees in those countries prior to commencement of recruitment.

Settings

To achieve the target sample size, it is necessary to recruit participants from multiple NICUs. Eligible NICUs are located in countries where the culture reflects what could be considered a "social support" society, where parents are consistently present in the NICU. Eligible NICUs also need to have staff possessing the necessary scientific and clinical expertise to conduct the trial. Current partner sites are located across five countries in Europe, the Middle East, and Latin America (Argentina, Colombia, Israel, Norway, Poland), and include eight NICUs (see trial registration data at ClinicalTrials.gov for an updated list). The number of beds in each NICU ranges from 13 to 60.

Eligibility criteria

Participants deemed eligible for the trial will meet the following criteria: *Infants:* Born below 35 weeks GA, of both genders, any ethnicity, from single or multiple pregnancies, and whom the NICU clinical staff judges to be sufficiently medically stable to start MT, and to likely require longer than 2 weeks of hospitalization from the time of recruitment. In multiple pregnancies, only the first-born infant who achieves medical stability will be included and randomized, while remaining siblings can receive the same interventions for ethical and practical reasons. Infant hearing screenings typically take place prior to discharge from the NICU, thus hearing status may not be known at time of study recruitment. Results of infant hearing screening at discharge will be tracked when available, to facilitate follow-up analysis, but infants who test positive for hearing impairments will still be included in data analysis due to the potential for infant and parent benefit despite such sensory impairment. *Primary caregivers*: One of the parents/caregivers must provide written, site-specific informed consent before any study procedures occur. Primary caregivers should agree to engage in at least 2 of the 3 MT sessions per week during NICU, and/or in 5 of the 7 MT post-discharge sessions. Primary caregivers should live within reasonable commuting distance from the treating NICU and should have sufficient understanding of the respective national language(s) to answer the questionnaires and participate in MT. Parents who are unable to complete the intervention and/or questionnaires, for example due to a mental illness, cognitive impairment, etc., will be excluded.

Interventions

The MT approach in this study is informed by models previously described and tested, including Creative Music Therapy with premature infants and their parents [26, 41, 42], First Sounds: Rhythm, Breath & Lullaby [31, 43, 44], and other developmentally-appropriate and family-centered approaches to MT with premature infants and their families [27, 45, 46]. Like other MT models [41, 42], it is based on the notion that infants have a capacity to

communicate actively [47, 48]. As in some newer models, parents are highly involved and the therapeutic benefit is directed toward infant and parents alike [31, 41, 44, 46]. The approach here thus builds on an emerging consensus, but is more explicit in its adaption to developmental levels and emphasis on infant-parent mutual regulation [49]. Furthermore, unlike previous studies [38], MT is extended beyond the tertiary care setting to help with the transition to daily life and municipal care. MT focuses on supporting positive relationship formation within the infant-parent dyad by promoting beneficial mutual regulation, and includes psychotherapeutic support of the parents to promote their stabilization, self-regulation, bonding and restorative experience in alignment with trauma-preventive models [44, 50]. Key elements of the MT intervention appear in Table 1.

MT during NICU: Participants will be offered individual MT sessions 3 times/week for approximately 30-40 minutes/session, with a maximum of 27 sessions per infant (assuming a maximum NICU stay of 9 weeks). Time spent in active music making with the infant may be shorter than 30 minutes, depending upon infant readiness, and the remaining portion of the session will be devoted to providing psychotherapeutic support for parents and coaching them in how to use their voices therapeutically with their infants. MT will be provided for eligible infants once they achieve sufficient medical stability to begin MT, usually after 26 weeks postmenstrual age (PMA; defined as GA at birth plus the time since birth [40]). Use of live music will follow recommendations from the American Academy of Pediatrics Committee on Environmental Health [51] and the Consensus Committee on Recommended Design Standards for Advanced Neonatal Care [52], namely that noise levels within the NICU should remain below 45 dB (A weighted), with hourly maximum sound levels (Lmax) < 65 dBA, and no more than 10% of each hour (L10) > 50 dBA. Prior to the first MT session with the infant, the music therapist will meet with the parents to discuss MT and assess aspects that will inform the course of MT including: music preferences and history, cultural values related to

music, level of comfort with singing, infant signals and patterns, family strengths and needs, and any challenges and resources that the parents deem relevant. The music therapist will then explain basic elements of the procedures listed below, engage parents in musical demonstration and form a loose plan for how the parents and music therapist will begin MT with the infant. The music therapist will observe the infant during a period of handling (such as during diaper change or transition to parent's arms) in order to become more familiar with the infant's signals and tolerance of stimulation, and parents' modes of responding to the infant. Thereafter, a flexible protocol of procedures matched to infant PMA, familial/cultural preferences, and infant's demonstrated readiness to receive stimulation, will occur as individually-tailored MT sessions at bedside:

From approximately 26 to below 32 weeks PMA, cautious use of sung/toned voice will be the main focus. During MT, the infant may be: held in a static manner by the caregiver (e.g., skin-to-skin care), resting in his/her isolette with the portal door open, or resting in his/her basinet or bed. MT during skin-to-skin care will be encouraged, if skin-to-skin care is part of standard care and the infant tolerates it. The music therapist assesses the infant's needs and behavior state, and if appropriate for the infant, shows caregivers how to use basic touch and positioning (such as caregiver/therapist's hand lightly and statically placed on infant's chest or back, or hands cupped at infant's head and feet) and/or principles of facilitated tucking and midline alignment to promote physical containment, enable behavior state regulation, and prepare the infant for MT. Parents will hold their infant or provide basic touch and/or positioning, and will receive support or demonstration from the music therapist as needed.

Using toning or predominantly wordless singing voice matched to infant breathing patterns, facial expressions and movements [41, 42], while monitoring infant behavior state shifts and physiological responses, the music therapist demonstrates how to either pacify the infant to promote sleep or bring the infant to a quiet alert state, depending upon the infant's needs.

Specific pitches used may be matched to the pitch of infant vocalizations, if present, or selected to mask environmental noises, and will aim to be comfortably within the parent's vocal range [43]. When appropriate for the infant, simple melodies or songs of kin [31, 43] modified into an infant-appropriate style are matched to infant breathing rate, gesticulations and facial expressions, and engagement/disengagement cues, so that the music remains infant-directed. Caregivers are encouraged to lead the singing/toning as soon as they feel comfortable, while the music therapist simultaneously provides musical and/or coaching support. MT may occur during breastfeeding or other feeding attempts, if the parents desire it and the infant tolerates it, but MT will not occur during painful or sensorially-demanding medical procedures due to the risk of over-stimulation.

From 32 weeks to below 36 PMA, the use of MT centers around cautious use of infant-directed music with expanded sensory experience. This phase applies as soon as the infant demonstrates readiness to receive additional sensory stimulation, but not prior to 32 weeks PMA. Guidelines from the previous phase apply and are developed upon in this phase for infants who are ready for more than pacification. Culturally-relevant, caregiver-preferred songs are modified in an improvisatory manner by caregivers to match infant's breathing rate, engagement/disengagement cues, facial expressions and gesticulations, in order to facilitate a musical interplay between caregiver and infant [41, 42]. This interplay generally moves from more pacifying in nature to more dynamic and interactive as the infant reaches 36 weeks PMA. Musical interplay may include gentle dynamic touch to back of infant's head or along infant's back, depending upon the infant's tolerance. The musical interplay can be used to support the infant in a quiet alert state, if appropriate for the infant. Vocal inflection may be used to promote eye opening, eye contact, and responses to social cues (e.g., smiling, cooing). The infant-directed improvised interaction will be paced and modified according to infant responses and engagement cues, and will be reversed or paused in response to disengagement

cues. Conversely, for infants who have difficultly rousing for meal times, sessions can begin as described in "cautious use of sung/toned voice," with caregiver/therapist hand placed lightly and statically on infant's chest or back, or both hands/wrists lightly and statically cradling the sides of the infant and supporting the infant to align at midline. If the infant tolerates infant-directed singing in these positions, the caregiver/therapist can progress to include gentle rhythmic cues via light touch to coax the infant into a quiet alert state. If MT is used during breastfeeding attempts, rhythmic aspects of musical phrasing [53], and the addition of slightly stimulative vocal sounds can be matched to infant engagement/disengagement cues to support suck-swallow-breathe coordination and promote infant-parent mutual regulation [54]. The music therapist may use simple acoustic instruments (e.g., nylon string acoustic guitar, monochord) with single tones or simple accompaniment to accompany infant/caregiver during this phase, if the infant tolerates such additional stimulation without disengagement cues or physiological signs of overstimulation.

From 36 weeks PMA, MT will focus on expanded engagement in musical exchange. This phase applies when the infant demonstrates readiness to engage in increasingly more interactive levels of musical exchange. Caregivers interact musically with the infant, using vocal inflection and musical phrasing to encourage the infant to achieve a quiet, alert state and engage in eye contact, vocalization, and rudimentary social interaction, if appropriate for the infant. Depending upon infant readiness, caregivers may use their voices and physical positioning to promote auditory localization, auditory tracking, and eye contact; and their fingers and hands to promote reaching, grasping, and mouthing. The therapist will encourage the caregiver to adapt preferred lullabies and children's songs or to modify songs of kin [31, 43] in order to encourage musical dialogue with the infant, and the therapist may provide basic harmonic or melodic accompaniment as support.

Standard care during NICU: This will vary across countries, but will typically include necessary medical care and a limited amount of interventions to reduce stress among infants and to inform and promote safety in parents [55]. Components of standard care will be recorded at each site.

MT post-discharge from hospital: Infant-parent dyads will be offered 45-minute individual MT sessions, 7 times distributed across the first six months after discharge (2 times/month for the first month, and 1 time/month thereafter). These will occur at home, municipal child health centers, or follow-up clinics and comprise: (1) Verbal greeting and brief discussion of infant's progress (approx. 5 min). (2) Musical greeting of infant and caregiver, encouraging caregiver to participate (5 min). (3) Engagement in musical exchange following the procedures described in the "from 36 weeks" category above and incorporating adapted play songs, with therapist modelling musical engagement (approx. 10 min). (4) Discussion of current infant/parent challenges and strategies for using musical interactions to address these needs, with therapist modelling musical techniques to promote self-regulation or to facilitate musical interaction, depending upon needs identified by the caregiver (approx. 10 min). (5) Caregiver demonstration of techniques discussed during session (approx. 10 min). (6) Musical closure and reminder of planned timing for next visit (approx. 5 min). Any siblings may be involved if desired by the caregiver, and sessions will incorporate musical instruments and resources present in the home, if appropriate for the infant. Subsequent sessions will follow a similar sequence, adjusted to infant developmental level and ongoing needs. The therapist will work in close dialogue with those providing standard aftercare procedures, when possible.

Standard care post-discharge from hospital: This includes follow-up visits and preventive interventions in primary or specialist health care as needed. Preventive interventions during the first year of life are focused on growth/eating/nourishment as well as psychomotor/sensory development and also include a focus on families and bonding [55].

Standard care may include other early intervention methods of care with the exception of other MT approaches.

Training in study procedures: The site investigator at each site will maintain responsibility for assuring that the trial procedures are implemented as intended. Site investigators and music therapists received initial training on study procedures during an in-person, three-day training in June, 2018. In addition, site investigators, music therapists and other site research personnel received online follow-up training from core team members prior to the commencement of the study at their site. Music therapists will receive additional monitoring and feedback on their first two MT sessions from NICU phase and first session from post-discharge phase, using review of audio/video recordings obtained for subsequent evaluation of treatment fidelity. The core team will maintain dialogue with each site at least monthly during implementation of the study to assure adherence to the protocol, answer questions, and help problem-solve possible challenges.

Treatment guidelines for music therapy: MT during NICU and post-discharge phases are conducted in accordance with treatment guidelines established for this study. Guidelines are grounded in current evidence-based practices, experiences from the Norwegian feasibility study, and feedback from our User Advisory Group and Scientific Advisory Committee. These treatment guidelines are used in training the music therapists involved in the study, and help promote consistency of treatment implementation across study sites. The treatment guidelines articulate guiding principles underlying the intervention, delineate the level of variation that is acceptable, and provide illustrative examples of approaches. Implementation of the guidelines allows for individual tailoring to meet the needs of the infant and/or parents, and presumes a music therapist trained specifically in the use of MT for premature infants and their families. A published version of the treatment guidelines will be available as a separate paper.

Assessment of treatment fidelity: We will assess treatment fidelity in terms of treatment delivery and treatment receipt. A pre-determined selection of audio recordings from NICU MT sessions and video recordings from post-discharge MT sessions will be assessed for adherence to core elements of the intervention. Extent of adherence during treatment delivery will be assessed by music therapists reviewing recordings of their sessions and completing self-ratings, and external raters reviewing the same recordings to determine extent of adherence. Inter-rater reliability between the external raters will be evaluated, and degree of correspondence between the external and therapist self-ratings will be determined, as appropriate. We will evaluate fidelity in regard to treatment receipt by parental self-rating at the 6 month CA timepoint.

Outcomes

Unless indicated otherwise, all outcomes will be assessed at baseline; one to two days before discharge to home; at 6 months CA (end of MT; primary endpoint); and at 12 months of CA (Fig. 1, Fig. 2). All applicable outcomes (i.e. all that are scale-based) will be calculated as final values, but where baseline scores are available they will be included in the statistical models (see below). Data collectors and assessors will be trained in assessment procedures and blinded to participant allocation; success of blinding will be verified. For all self-report instruments we will use official translations, or if not available, we will translate according to recommended procedures with translations, back-translation and discussions before the final version is completed [56]. Psychometric properties of the instruments will be assessed across sites.

Primary outcome: Bonding between primary caregiver and infant at 6 months CA will be measured using the Postpartum Bonding Questionnaire (PBQ) [57, 58]; the same outcome will also be assessed at discharge and at 12 months CA. The PBQ is a parent-rated screening instrument for disorders of the early mother-infant relationship consisting of 25 statements on

a six-point Likert scale (each 0-5; sum score ranging from 0 to 125; high = problematic), addressing problems in the mother-infant relationship based on weakened bonding; rejection and anger; anxiety about care; and risk of abuse [59]. The scale is validated and widely used in clinical practice and research [39]. It has been translated and tested in several languages and cultures [58] and has been found to be reliable in mothers with or without depression or bonding problems [59]. Results from feasibility testing and user feedback in Norway confirmed the acceptability and relevance of the PBQ, also in comparison to alternative but less widespread measures that were considered. The scale covers both the more common and the rare but important problems that parents and infants can have.

Secondary infant outcomes will be as follows.

(1) The most important among the secondary outcomes is *child development* at 24 months of CA, as indicated by the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III). The Bayley-III is considered the gold standard for assessing development in young children up to 42 months [60]. At 24 months the tool is used routinely in many countries for extremely premature infants. Assessors will be trained and reliability-tested before conducting the assessments for this study, also in cases where the assessments are part of routine procedures, when possible. The three main composite scores of the Bayley-III are cognitive, language (receptive and expressive), and motor (fine and gross motor) development; each of the scales is standardized with a population mean of 100 (SD 15), with higher scores indicating better development. No total score covering all domains is available, but the most important areas for the present study will be language and cognition. The Bayley-III has US norms and has been used extensively for developmental assessments for premature infants (e.g. [61]).

(2) Infant development at 6 and 12 months CA will be assessed by the Ages and Stages Questionnaire, 3rd edition (ASQ-3) [45]. The ASQ-3 is an age-specific parent-reported

screening questionnaire consisting of 30 items covering five developmental domains with five subscales: communication, fine-motor, gross-motor, problem-solving, and personal-social (possible range 0 to 60) and a total score (possible range 0 to 300), with higher scores indicating better development.

(3) Infant socio-emotional development will be measured by the Ages and Stages Questionnaire Social-Emotional (ASQ:SE) at 6 and 12 months of CA. This is a parent-completed questionnaire with 19 or 22 Likert-scaled items (each 0-5-10), plus additional items for whether an item is of concern to the parent (each 0-5), resulting in a score ranging from 0-285 or 0-300, at 6 and 12 months respectively. Lower scores indicate better socio-emotional development [47, 48].

(4) Re-hospitalization during the first year of life (excluding outpatient visits), based on electronic health records or parent reports. This will be calculated as the time from initial discharge until first re-hospitalization.

Secondary parental outcomes include the following.

(1) Maternal depressive symptoms will be assessed with the Edinburgh Postnatal Depression Scale (EPDS) at baseline, 1-2 days prior to discharge, and at 6- and 12- months of infant CA. The 10-item validated self-report instrument assesses mothers' postpartum depressive symptoms, excluding somatic symptoms of depression that are common in new mothers (such as loss of energy, feeling tired, changes in appetite and sexual drive)[62]. Scores can range from 0 to 30, with high scores indicating more depressive symptoms.

(2) Level of anxiety (both mothers and fathers) will be assessed with the Generalized Anxiety Disorder Assessment (GAD-7) at baseline, 1-2 days prior to discharge, and at 6- and 12-months of infant CA. The self-report 7-item questionnaire serves as a screening tool and severity measure for generalized anxiety disorder [63]. Scores can range from 0 to 21, with higher scores indicating higher anxiety.

(3) Level of parental stress (both mothers and fathers) will be assessed with the Parental Stress Scale (PSS) at 6- and 12- months of infant CA. This is a self-report 18-item questionnaire that assesses stress associated with parenting [64]. Scores can range from 18 to 90, with higher scores indicating higher stress.

Other measures: Specific *medical and social factors* relevant for subgroup analyses will include parents' socioeconomic status (collected at baseline), infants' hearing status (collected at discharge), frequency of skin-to-skin care during NICU, and experience of breastfeeding prior to 6 months CA. Additional open-ended questions will address other potential factors that might impact infant responsiveness (which may include e.g. intraventricular hemorrhage, metabolic disturbances, or genetic disorder among infants, and known mental health or substance use problems of parents). These will be drawn from hospital records and may be supplemented by parent self-reports.

Cost-effectiveness

We will explore and collect data necessary for analyzing cost-effectiveness both from a health services perspective (i.e. costs of all treatments incurred within the health sector including the costs of MT and standard care) and from the broader societal perspective (i.e. including all treatments incurred by the health sector and other indirect costs such as productivity losses and out-of-pocket expenses incurred by the parents). If clinical effectiveness is found, we will apply for separate funding to explore the additional cost to achieve a unit improvement in parent-infant bonding and explore the likelihood MT will be good value for money. This will be done through incremental cost-effectiveness ratios and willingness to pay analyses. Otherwise, these data will be used to describe the context in which the treatment took place.

Adverse events

All significant harms as well as unintended effects for each group will be collected and described by the site investigator, and reported to the core team. All adverse events that site

investigators suspect may be related to MT and all serious adverse events will be reported to the Data and Safety Monitoring Committee by the core team. A special form to report trial-related adverse events has been developed and distributed.

Sample size and power calculation for the main comparison

No previous RCT examined effects of MT on the PBQ; two small RCTs [38] and a recent non-randomized study [46] examined mother-infant bonding, but provided insufficient data for meta-analysis. Studies using the PBQ with other interventions found effects ranging widely from around 0.25 to 9.0, with SDs ranging from 4 to 12 [11, 65, 66]. Assuming a difference of 4 points on the PBQ (SD = 8) as a minimal clinically important difference for this study, power of 80% will be achieved for each main effect (each tested on a two-sided 2.5% significance level, i.e. 5% with Bonferroni correction for two tests) with a sample size of 155. Taking into account some clustering by country (ICC 0.01; 5 countries), this is increased to 203. To allow for 20% attrition, we will aim to include 250 infants (approximately 50 in each country) and their parents. This sample size will also ensure power for testing proportion differences of about 15% (e.g. binary analysis of problematic bonding; re-hospitalization).

Special considerations are needed for multiple pregnancies (twins, triplets, etc.), which account for about 2% of all pregnancies in the Hordaland region of Norway [67], but are more commonly encountered in NICUs due to elevated risk of preterm birth. Although including all siblings would serve to increase the sample size, it may lower the resulting power due to cluster effects. Therefore, we will only formally enroll and analyze the first-born sibling of each multiple pregnancy, although all multiples can receive the allocated intervention (see Eligibility criteria).

Recruitment

Recruitment at the first site commenced in July 2018, and completion of recruitment is planned for the end of 2019. Enrollment will be completed in the NICU by a trained member of the unit staff according to the eligibility criteria. The staff person will be responsible for first contact with caregivers, providing an opportunity for informed consent. We estimate that an 18-month period for recruitment will be sufficient to achieve the targeted sample size. Each site will be encouraged to recruit approximately 50 infants and their parents; therefore, slow recruitment at some sites will be tolerable. Recruitment rates will be monitored carefully. Local and national partners responsible for primary care provision will serve as contact points after discharge and will be actively involved, wherever possible. Once an infant is randomized, the site investigator will make every reasonable effort to follow the infant and the parent/caregiver for the entire study period of 24 months. The site investigator will be responsible for developing local standard operating procedures for the site, in order to facilitate implementation of all aspects of the study. In addition, site investigators will develop post-recruitment retention strategies to promote retention (e.g., development of a newsletter directed to participants).

Randomization and allocation concealment

After site-specific informed consent and baseline assessment, participants will be randomly assigned to MT during NICU or standard care using a computer-generated randomization list, with ratio 1:1, in blocks with sizes of 2 or 4 varying randomly, stratified by site using an online system. The random allocation sequence will be generated and administered by people with no involvement in the clinical work to ensure allocation concealment. One potential issue with providing MT in shared NICU rooms is contamination. Parents may pick up strategies from other parents in the same room (or, likely to a lesser extent, from other parents or staff on the ward). We will assess contamination through the following questions at the end of each parent's participation in the study: "How often did you sing or play music with or for

your child (daily/weekly/occasionally/never)? If so, in what way (please describe)? Did you learn from another parent in the NICU about using music (yes, please describe/no)?"

Before discharge to home, participants will be randomized a second time to post-discharge MT or standard care in a 1:1 ratio, using the same procedures. This two-step randomization was chosen as the best way to create balance among those remaining in the study for the post-discharge phase, and to avoid differential drop-out in the NICU phase due to expectations for the post-discharge phase. We will assess potential contamination in the post-discharge phase by asking participants if they engaged in MT with their infant outside of the study during the first year of the infant's life, and if so, the frequency and nature of such engagement.

Blinding

Due to the nature of the intervention neither participants nor staff can be blinded to allocation, but are reminded not to disclose the participant's allocation status to outcome assessors. All outcomes that are not self-reports will be conducted by an assessor blind to treatment allocation, and success of blinding will be tested by asking assessors.

Data analyses

Baseline analysis: Sociodemographic and clinical baseline properties for the groups will be characterized by descriptive methods (mean (SD), median [range], n (%)).

Primary analysis: We will use an intention-to-treat (ITT) approach using all available data from all participants as randomized, regardless of the intervention actually received. Multiple imputation will be used for missing data, if applicable [68].

Effects will be examined by testing the randomized groups for differences in the primary endpoint (t-test or Mann-Whitney; change in PBQ scores to 6 months CA), as well as by fitting linear mixed models. In the first modeling step we will assess the effect of the first randomization (Fig. 1) using the following model:

$$PBQ_{it} = \beta_0 + \beta_1 time_t + \beta_2 gr_i + \beta_{12} time_t gr_i + U_i + \varepsilon_{it} \ ,$$

where PBQ_{it} denotes the PBQ score for participant i at measurement t, $time_t$ the time from baseline at measurement t and gr_i the randomization group of participant i. β_0, β_1, β_2 and β_{12} are the coefficients estimated in the model, U_i is an individual random term per participant and ε_{it} an independent, identically distributed error term. In the second step we refine the model to take into account both randomization steps, leading to the extended model:

$$PBQ_{it} = \beta_0 + \beta_1 time_t + \beta_2 grR1_i + \beta_{12} time_t grR1_i + \beta_3 grR2_i + \beta_{13} time_t grR2_i + U + \varepsilon_{it} ,$$

with the same notation as above and $grR1_i$ and $grR2i$ denoting the groups from the first and second randomization, respectively. In these models β_1 describes a group-independent time effect, β_2 and β_3 a time-independent group effect, and β_{12} and β_{13} the time-dependent change of the group effect. We will investigate both linear and simple contrasts (comparing each time point with the baseline) in time to assess the treatment effect.

Secondary analyses: The same analyses will be done for the secondary outcomes; using an analogous generalized linear mixed model for binary outcomes. Per-protocol analyses will include those who received at least 6 MT sessions in the NICU and at least 5 MT sessions post-discharge, respectively; these are considered the minimum numbers for the intervention to be successful.

Subgroup analyses: Additionally, we will conduct exploratory statistical analyses for pre-specified subgroups: sex; GA at birth [<28 wks, 28 to <32 wks, 32 to < 35wks]; hearing status at discharge [normal vs. abnormal]; bonding at baseline [PBQ impaired bonding score ≥ 11 vs. <11]; parental socioeconomic status [poor vs. other] [69]; average parental skin-to-skin care during NICU [4 or more days per week vs. fewer than 4 days per week]; duration of breastfeeding prior to 6 months CA [none, fewer than 3 months, 3 months or greater]; perceived emotional closeness during breastfeeding [consistently, sometimes, rarely]; as well as qualitative/mixed-methods analyses of process data to maximize learning.

Data management and collection methods

In order to maintain participant confidentiality all information will be stored with ID code numbers. The ID code numbers will be unrelated to participants' identifiers, except in a central file with the participants' contact details. All data will be stored on an electronic database management system located on a secure server with password-controlled access provided for research data collectors.

To ensure data quality, a trial database will be set up and maintained using a safe server (Uni Research Health Data Storage, UHEADS; now maintained by NORCE) and OpenClinica software. UHEADS is a system for safely storing health research data that accommodates the safe upload, storage and retrieval of any sensitive research data. OpenClinica is a web-based system for electronic data capture and clinical data management for multicenter clinical trials, which conforms to relevant international standards for health research. NORCE Norwegian Research Centre AS runs an open source version of OpenClinica. A manual for using OpenClinica in this study has been created and distributed to collaborators. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records identified by the ID code number. All study-related information on paper, including questionnaires, and administrative forms will be securely stored in locked file cabinets in areas with limited access.

Data availability statement

After completion of the study period, de-identified individual participant data of the main variables will be stored on a publicly available repository to ensure replicability and transparency, namely Norwegian Centre for Research Data (NSD).

Monitoring

The site investigators will practice entering data so that the core team can confirm that site investigators are proficient in all aspects of data entry, query response, and communication with the team at each site. Uploaded data will be regularly checked by a core team researcher

in order to ensure good quality data. Monitoring will follow a risk-based approach, with site investigators and core team members sharing the responsibility for quality and completeness of data. Core team members will conduct monitoring of source documents via scan of randomly chosen questionnaires at all enrolling LongSTEP sites, and will conduct on-site monitoring visits as needed. Through these on-site visits we will audit the overall quality and completeness of the data, examine source documents and interview coordinators to determine whether data reported in OpenClinica are complete and accurate, and whether the clinical site has complied with the requirements of the protocol. If a problem is identified, the core team will assist the site investigator in resolving the issues.

Oversight, auditing, and advisory committees

Data and Safety Monitoring Committee (DSMC): An independent panel of three clinicians and methodologists with relevant expertise but no direct involvement in the trial has been established to ensure research integrity and safety of participants in the trial. After an initial protocol review meeting, the DSMC will check the general progress of the clinical trial including recruitment and completeness of follow-up; safety; and any other unforeseen events. To this end, the DSMC will receive updated reports from the project statistician, which may be unblinded with respect to intervention arms. Other project team members will not have access to such unblinded reports and will not attend the closed part of the DSMC meetings where such content is discussed. No interim efficacy analysis is planned for this trial.

Trial Steering Committee (TSC): The TSC will consist of one representative from each recruiting site, two user representatives, and two representatives from the core team. It will monitor trial progress, will receive recommendations from the DSMC, and will be involved in all decisions about protocol amendments or other changes in the trial.

User Advisory Group (UAG): An advisory group consisting of parents of premature infants in Norway has been established for this study. This group is important for eliciting user feedback and ensuring relevance of the study, including any protocol amendments, as well as helping to ensure efficient recruitment and dissemination strategies. Similar involvement of users in other countries will be encouraged.

Scientific Advisory Committee (SAC): An international group of clinicians and researchers with relevant clinical expertise was established during project development and will continue to advise on various aspects related to development and implementation of the study. The panel includes experts in areas such as MT, neonatology, and psychology.

Research ethics approval

The project as a whole received ethics approval from The Regional Committees for Medical and Health Research Ethics (2018/994/REK Nord, date of approval: 03 July 2018). In addition, each participating site must secure local ethical approval prior to commencing recruitment. Site-specific written informed consent will be obtained postnatally following routine practices in the NICU. A trained staff of the trial will inform parents/caregivers about the study and provide an opportunity for informed consent. The parent/caregiver will receive written and oral explanation of the proposed research project, including information regarding the research project, the aims of the project, the duration of the participant's involvement, the expected benefits to the participant and others, the nature of the intervention, and the procedures involved in participation. It will be emphasized that enrollment in the study is voluntary, that parents/caregivers can withdraw at any time from all or part of the study, and that any decision they take in this respect will have no bearing on the medical care received. Additionally, it we be highlighted that information generated by the study will be published, but that no details will be divulged from which the participant could be identified. Primary

caregivers will be informed of whom to contact in an emergency, and the staff will be available to answer questions.

Dissemination

Dissemination of the findings will apply to local, national, and international levels. Aspects related to the feasibility of implementing MT in the hospital and in primary care and region-specific and culture-specific aspects of treatment implementation will be submitted to corresponding specialized interdisciplinary journals. Main results of the trial concerning clinical effectiveness will be submitted to a leading medical journal. Additional results of exploratory statistical analyses and qualitative/mixed-methods analyses of process data will be published in specialized international journals. Beyond journal publications, we will disseminate results through presentations at national and international conferences. Popular dissemination, particularly to users, their families, user organizations, health services, and the general public will be achieved via a periodic newsletter, educational brochures and/or popular press articles.

Discussion

Controlled research on the impact of MT for premature infants and their caregivers demonstrates short-term improvements in infant physiologic and behavior states, feeding behavior, and length of hospital stay, as well as decreases in parental distress and anxiety [31, 34, 38]. LongSTEP fills a critical gap in knowledge by providing MT over a longer term from hospitalization through the first six months of life, and by assessing long-term outcomes of MT for both infant and parents during the first two years of the infant's life.

Since MT for premature infants and their caregivers is an emerging area of practice and research within Scandinavia, this study aims to integrate best available evidence from international developments with standards of practice existing in specific national health care environments, to create a model of care that is culturally-relevant for social support societies. LongSTEP consists of MT with a high level of parental engagement during the course of NICU hospitalization and a support- and consult-to-parent model of MT for the first six months following discharge. The model enables parents to assume a central role in the care of their infant, with the music therapist providing support and coaching to help parents to use their innate resources to promote developmentally-appropriate mutual regulation of the parent/infant dyad, improve quality of interaction and enable healthy bonding during this vulnerable time. The long-term aim is to assure healthy infant-parent relation and improve child developmental outcomes and promote parental psychological well-being over the first two years of the infant's life.

The pragmatic nature of this trial and its high clinical applicability are reflected in several dimensions, as described in the pragmatic-explanatory continuum indicator summary (PRECIS) [70]. Eligibility criteria are designed to be as inclusive as possible to promote applicability of the evidence with respect to a broad population. Broad inclusion criteria ensure enrollment of participants with heterogeneous characteristics similar to those seen by

clinicians in daily practice, and exclusion criteria are narrow and exist only to ensure infant safety. Another pragmatic dimension of this trial is flexible MT delivered by a qualified music therapist. MT is tailored to infants over a broad range of PMA and also incorporates family and cultural preferences. Additionally, we do not restrict if or how co-interventions will be delivered. Participants in all arms will receive standard care. Analysis of primary outcome will include all individuals regardless of compliance in order to test if the intervention works under usual conditions, with all the noise inherent therein.

As a limitation it should be noted that our primary outcome measure is a self-report tool that is completed by parents who know which intervention they and their infant received. It is an inherent challenge within MT research that we cannot blind participants and providers, as they are aware that they have received MT. We believe that mothers' subjective perception of their bond with their infant is an important phenomenon to evaluate and target with supportive intervention. We hope to offset the use of a self-report primary outcome completed by non-blinded participants by including the Bayley-III to provide an observational evaluation of infant development completed by independent, blinded outcome assessors.

Clinical benefits as well as resulting societal benefits related to disability prevention and economic outcomes are likely to occur over a longer term. To address this, we will also include the possibility in the consent forms to collect later follow-up data, but these will be beyond the present project. In summary, this pragmatic trial will determine the effects of MT under usual conditions, and the design as a multicenter trial will further ensure wide generalizability.

The project's social impact includes filling gaps in knowledge regarding the long-term impact of MT with preterm infants/caregivers, including highly user-relevant outcomes. The high applicability of this trial will facilitate ongoing development of evidence-based care for preterm infants. Opportunities for improved training of music therapists and effective

implementation of MT in neonatal care will apply both to countries where MT in this area is new and to countries that already have a more established foundation. Specifically, LongSTEP will make a unique contribution to continuity of care by bridging intervention from NICU hospitalization to municipal and home settings post-discharge. In addition, LongSTEP fosters interdisciplinary collaboration between specialist and primary/municipal health care services (psychologists, nurses, physicians, music therapists).

In conclusion, LongSTEP builds off of evidence-based practice in neonatal MT, which supports the use of infant-specific MT tailored to developmental level and provided in conjunction with primary caregivers. The project will advance previous knowledge by suggesting a pathway by which MT can promote infant development while also improving parental psychological outcomes. Coaching parents in the use of music may help improve infant regulation and decrease parental stress during parent/infant interactions, which in turn may promote bonding and contribute to better infant developmental and parental psychological outcomes.

Abbreviations
ASQ-3 – Ages and Stages Questionnaire (3rd edition); ASQ:SE – Ages and Stages Questionnaire: Social-Emotional; PBQ – Postpartum Bonding Questionnaire; Bayley-III – Bayley Scales of Infant and Toddler Development (3rd edition); EPDS – Edinburgh Postnatal Depression Scale; CA – corrected age; GA – gestational age; GAD-7 – Generalized Anxiety Disorder Assessment; MT – music therapy; NICU – neonatal intensive care unit; PMA - postmenstrual age; PSS – Parental Stress Scale; RCT - randomized controlled trial.

Ethics approval and consent to participate
The Regional Committees for Medical and Health Research Ethics (2018/994/REK Nord, date of approval: 03 July 2018) approved of the main study. A protocol for feasibility trials in Norway and Poland was approved by the Regional Committees for Medical and Health Research Ethics (2017/2249/REK Nord, date of approval: 05 December 2017) and the Research Ethics Board at the University of Gdańsk (no 3/2018, date of approval: 12 April 2018), respectively.

Consent for publication – Not applicable.

Availability of data and material – Not applicable.

Competing interests
ME, TG, CGh, and CGo are clinically trained music therapists. The other authors declare that they have no competing interests.

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Table 1. Key elements of the music therapy intervention

Phase of intervention	Key elements	Intervention description
All phases	High parental/caregiver involvement and resource-oriented	Parents/caregivers are recognized as possessing inherent resources that can aid their infant and themselves following premature birth. In all aspects of the MT intervention, parents are encouraged to take a leading role, while receiving support from the music therapist.
	Therapeutic benefit aimed at infant-parent dyad/triad	MT promotes infant-parent mutual regulation and includes psychotherapeutic support of parents.
	Neurodevelopmentally appropriate	Specific use of MT is matched to infant PMA, familial/cultural preferences, and infant's readiness.
	Positioning to promote beneficial mutual regulation	Infant/parent positioning is considered a vital component for promoting beneficial self-regulation.
	Based on needs of infant/parent(s) in the moment	Infant and family needs are assessed at the beginning of each intervention phase (during NICU and post-discharge), and during each MT session to assure that use of MT matches needs in the moment (e.g. promoting sleep vs. encouraging quiet alert interaction).
	Parental voice as foundation for infant-directed use of song	Parents' use of their sung (and when necessary, spoken) voice along with positioning and physical presence forms the foundation of an attuned response to their infant. Parents' sung voice, facial expressions and vocal expressions vary in response to infant's engagement/disengagement cues, breathing rate, gesticulations and facial

		expressions, so that the music remains infant-directed.
Infant medically stable, in NICU, 26 to below 32 wks PMA	Cautious use of sung/toned voice	Predominantly wordless singing voice is matched to infant breathing patterns, facial expressions and movements, and either promotes sleep or a quiet alert state depending upon infant's needs.
	Incorporation of familiar songs adapted for the premature neonate	Parents learn how to adapt songs that are familiar/preferred so that they are appropriate for the preterm neonate (e.g. simplified and/or transformed into lullaby style).
Infant medically stable, in NICU, 32 wks to below 36 wks PMA†	Cautious use of infant-directed song with expanded sensory experience	Culturally-relevant, caregiver-preferred songs are adapted in the moment to match infant breathing rate, engagement/disengagement cues, facial expressions and gesticulations, to promote musical interplay when appropriate for the infant. The musical interplay may include dynamic touch, and parents' use of vocal inflection and phrasing to promote rudimentary musical dialogue, eye contact and social responses.
	Addition of rhythmic cues and musical phrasing cues to support feeding attempts	By adapting familiar songs, rhythmic aspects of musical phrasing, and the addition of mildly stimulative vocal sounds can be matched to infant engagement/disengagement cues to support suck-swallow-breathe coordination and promote mutual regulation.
	Accompanying instruments are used to support the dyad/triad, with complexity matched to infant readiness	The music therapist may use acoustic instruments (e.g. nylon string acoustic guitar, monochord) to provide single tones or simple accompaniment to support

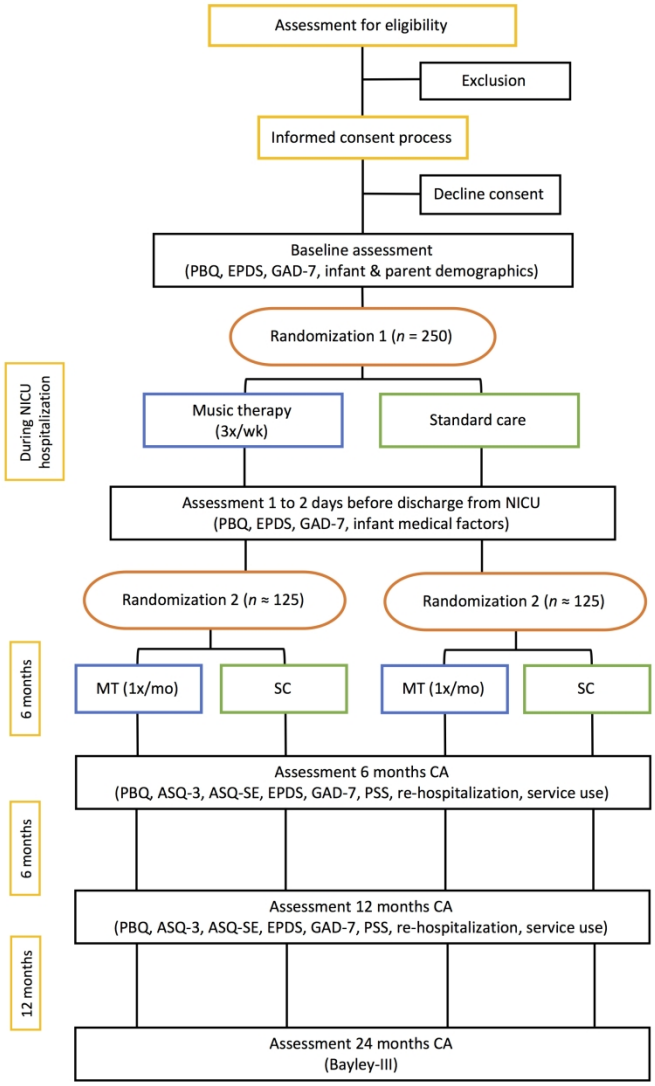
		infant/parent, if infant tolerates the added musical stimuli well.
Infant medically stable, in NICU, from 36 wks PMA	Expanded engagement in musical exchange	Parents adapt preferred songs so that vocal inflection and musical phrasing reflect infant responses and promote eye contact, vocalization and rudimentary social interaction, if appropriate for the infant. Parents may also use their positioning while singing to promote auditory localization, auditory tracking or eye contact.
Post-discharge from NICU	Based on needs of infant/parent(s) in the moment and in relation to recent challenges	Infant and family needs are assessed at the beginning of each MT session, and particular strengths and challenges that have arisen in the past 2 weeks are identified and targeted (e.g. transitioning between behavior states, maintaining alertness during feeding, experiencing rewarding relation).
	Expanded engagement in musical exchange, including adapted play songs, when appropriate	Parents engage in and expand upon musical approaches from the previous phase, matched to infant/family needs, and music therapist models variations and adaptations as needed.
	Identification of musical resources that may help address current challenges or build upon current strengths	Parents and music therapist brainstorm how music can be adapted and used for infant/family needs, and parents have a chance to try out certain approaches with support, if appropriate.

† Elements of the prior phase apply to subsequent phases. An infant remains in the previous phase (despite PMA) until ready to receive more expanded stimulation. The combination of elements used within each phase will depend upon the infant's needs in the moment.

Figure captions

Figure 1. Flow of participants though the study: Illustration of the study design
Note. ASQ-3 – Ages and Stages Questionnaire (3rd edition); ASQ:SE – Ages and Stages Questionnaire: Social-Emotional; Bayley-III – Bayley Scales of Infant and Toddler Development (3rd edition); CA – corrected age (chronological age reduced by number of weeks born preterm); EPDS – Edinburgh Postnatal Depression Scale; GAD-7 – Generalized Anxiety Disorder Assessment; PBQ – Postpartum Bonding Questionnaire; PSS – Parental Stress Scale.

Figure 2. Schedule of enrollment, interventions, and assessments
Abbreviations: ASQ-3 – Ages and Stages Questionnaire (3rd edition); ASQ:SE – Ages and Stages Questionnaire: Social-Emotional; Bayley-III – Bayley Scales of Infant and Toddler Development (3rd edition); CA – corrected age (chronological age reduced by number of weeks born preterm); EPDS – Edinburgh Postnatal Depression Scale; GAD-7 – Generalized Anxiety Disorder Assessment; PBQ – Postpartum Bonding Questionnaire; PSS – Parental Stress Scale.



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	STUDY PERIOD						
	Enrollment	1st random-ization	Post 1st allocation	2nd random-ization	Post 2nd allocation		
TIMEPOINT	*before random-ization*	0	*during NICU stay*	*at discharge from NICU*	*6 months CA*	*12 months CA*	*24 months CA*
ENROLLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X		X			
INTERVENTIONS:							
MT		←	—	→ ←	—		
Standard care		←	—	—	—	—	→
ASSESSMENTS:							
infant / parent demographics	X		X				
PBQ; EPDS; GAD-7	X		X		X	X	
ASQ-3; ASQ:SE; PSS					X	X	
Bayley-III							X
Re-hospitalization				→ ←	—	—	
Adverse events		←	—	—	—	—	

Schedule of enrollment, interventions, and assessments
Abbreviations: ASQ-3 – Ages and Stages Questionnaire (3rd edition); ASQ:SE – Ages and Stages Questionnaire: Social-Emotional; Bayley-III – Bayley Scales of Infant and Toddler Development (3rd edition); CA – corrected age (chronological age reduced by number of weeks born preterm); EPDS – Edinburgh Postnatal Depression Scale; GAD-7 – Generalized Anxiety Disorder Assessment; PBQ – Postpartum Bonding Questionnaire; PSS – Parental Stress Scale.

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SPIRIT 2013 Checklist for the LongSTEP project: 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	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	32
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	1
	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	2; 32
	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)	26-27

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	5-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7-8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10-11
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)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-16; Table 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)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	17-18
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	16-17
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	18-21
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)	10; Fig. 1; Fig. 2

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	21
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	22-23
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	23-24
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	23-24
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	23-24
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	24
	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	18; 25-27
	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	23

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	25-26
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	24-25
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	25
	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)	24-25
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	26-27
	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	27
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; 26-27
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	26-27
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3; 10-11; 27-28; 32
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)	27

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21-22; 27-28
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	25-26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	32
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	n/a
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	28-29
	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	26
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Available on 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.