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Creative Music Therapy in Newborns with Congenital Heart Disease: A Randomized Clinical Trial – BOND Study

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Category A
Study Registration:	The study will be registered on ClinicalTrials.gov. Additionally, registration in the Swiss National Clinical trial Portal (SNCTP via BASEC) will be performed
Study Identifier	BOND Study
Sponsor-Investigator:	Prof. Dr. med. Cornelia Hagmann Head of the Neonatal Unit Department of Intensive Care and Neonatology University Children's Hospital Zurich – Eleonore Foundation Steinwiesstrasse 75 CH-8032 Zurich phone +41 44 266 35 27 Cornelia.Hagmann@kispi.uzh.ch
Investigated Intervention:	Standard care versus creative music therapy in newborn infants with congenital heart disease
Protocol Version and Date:	Version 1.3 (dated 21/07/2022)

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PROTOCOL SIGNATURE FORM

Study Title	**Creative Music Therapy in Newborns with Congenital Heart Disease: A Randomized Clinical Trial** **BOND Study**

The Sponsor-Investigator has approved the protocol version 1.3 (dated 21/07/2022) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor-Investigator:

Name: Prof. Dr. med Cornelia Hagmann

Date: 21. 7. 2022 Signature: C. Hagmann

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
ASS	*All Survivors Set*
BASEC	*Business Administration System for Ethical Committees*
CHD	*Congenital Heart Disease*
ClinO	*Ordinance on Clinical Trials in Human Research*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
CTM	*Creative Music Therapy*
eCRF	*electronic Case Report Form*
FADP	*Federal Act on Data Protection*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act*
ICH	*International Conference on Harmonisation*
NICU	*Neonatal Intensive Care Unit*
OXT	*Oxytocin*
PCERA	*Patient-Child Early Relational Assessment*
PCHD	*Parents of Infants with CHD*
PICU	*Pediatric Intensive Care Unit*
PTSD	*Posttraumatic Stress Disorder*
PPS	*Per Protocol Set*
SAE	*Serious Adverse Event*

1 STUDY SYNOPSIS

Sponsor-Investigator	Prof. Dr. med. Cornelia Hagmann
Study Title	Creative Music Therapy in Newborns with Congenital Heart Disease: A Randomized Clinical Trial
Short Title / Study ID	BOND Study
Protocol Version and Date	Version 1.1 (dated 22/03/2022)
Study Registration	The study will be registered on ClinicalTrial.gov Additionally, registration in the Swiss National Clinical trial Portal (SNCTP via BASEC) will be performed
Study Category and Rationale	Other clinical trials category A, according to Swiss Human Research Act. In the context of a clinical trial, we will evaluate if parent-infant interaction can be improved by a family integrated, individualised, interactive resource- and needs-oriented music therapy approach in the dyads of infants with congenital heart disease and their parents. This intervention will be compared with the standard of care. The trial is considered to entail minimal risks and burdens.
Background and Rationale	Congenital heart disease (CHD) is the most common birth defect, with a rate of 8 per 1000 live births. With increased medical advances within the last decades, most children with CHD who undergo open-heart surgery survive into adulthood, defining CHD as chronic disease. A high level of stress/distress, anxiety and depressive symptoms experienced by the parents are the result of their infant's cardiac diagnosis and hospitalization, furthermore infants may be immediately separated from their parents after birth, causing an alteration in the normal bonding process and parental role. Due to psychological stress mothers of CHD children report difficulties in establishing mother-infant bonding. Failure to establish this bond during infancy can have serious long-term effects on the mother-child relationship and affect the child's development. Creative music therapy (CMT) is an individualized, resource- and needs-oriented music therapy approach, which aims to promote parental self-confidence, competence and autonomy and enhances the parent-infant bonding process. The main aim of this interventional randomized trial is to evaluate if parent-infant interaction, parental mental health and child's outcome can be improved by CMT.
Risk / Benefit Assessment	This is a non-pharmacological intervention which has no associated risks.
Objective(s)	1. Investigate whether CMT improves mother-infant interaction assessed at age 6 months 2. Investigate whether CMT improves parental mental health at discharge and age 6 months 3. Investigate whether CMT improves child outcome at age 6 months
Endpoint(s)	The primary endpoint is mother-infant interaction measured at age 6 months using the parental early child assessment (P1, PCERA). Secondary endpoints for parental outcome assessed by questionnaires: - Parental stress - Parental anxiety - Parental depressive symptoms - Father-infant interaction - Parental attachment Infant outcome assessed by - Brain Magnetic resonance imaging - The Infant Behavior Questionnaire Revised (IBQ-R), Infant Temperament - Fragebogen zum Schreien, Füttern und Schlafen
Study Design	This is an interventional, single-center randomized controlled clinical trial conducted in newborn infants with congenital heart disease.

Statistical Considerations	Eligible infants will be allocated 1:1 to music therapy and control, using block randomization with stratification by socio-economic score (SES, <8 vs >8) and risk of CHD according to the Risk Stratification for Congenital Heart Surgery. Analyses: (1) All patients randomized to the trial who survived until 6 months of age (all survivors set, ASS). We will exclude patients who died because we expect mortality to be independent of the trial intervention and thus to be similar in both groups. This set will be analyzed according to the intention-to-treat principle, using multiple imputation of missing data. (2) All patients in the ASS who were treated per protocol (per protocol set, PPS). Treatment per protocol will be defined as a minimum of ten CMT sessions
Inclusion- / Exclusion Criteria	*Inclusion Criteria*: All newborn infants with CHD born >35 weeks of gestational and <28 days at diagnosis of CHD irrespective of severity of the heart disease and admitted to NICU/PICU at the Children's University Hospital. Infants with syndromes and /or confirmed chromosomal abnormalities will also be included. *Exclusion Criteria:* Gestational age at birth <35 weeks, age >28 days at diagnosis of CHD
Number of Participants with Rationale	Total patient 164, 82 per trial group. To ensure a power of 80 % at a significance level of 5 %, we would need a total of 130 evaluable patients. Considering a drop-out rate of 20 % (mortality, lost to FU assessment, drop-outs), a total of 164 infants will need to be recruited, 82 per group.
Study Intervention	Standard care and creative music therapy 3x20 minutes per week during admission, at least 10 session during admission, after discharge once every other week until 6 months of age.
Control Intervention	Standard care
Study procedures	Study coordinators will screen all infants for eligibility each day on our neonatal and pediatric intensive care units. If eligible, they will get in contact, inform and consent the parents within the first week of admission. Randomization (1:1) into intervention (CMT) or standard of care will be done by the study coordinators. We will record the demographic and clinical data according to the existing ORCHID registry, which is a prospective registry for infants with CHD requiring neonatal surgery. We record the frequency of involvement of other than medical and nursing personals such as psychologists/psychiatrists, social workers, breastfeeding counselor, speech therapist, nutritional counselor and physiotherapists. All data will be recorded with an eCRF in a RedCap database.
Study Duration and Schedule	4 years in total, with a recruitment period of about 3 year. Planned 07/2022 of First-Participant-In Planned 07/2025 of Last-Participant-Out
Sponsor-Investigator	Prof. Dr. med. Cornelia Hagmann Head of Neonatal Unit Department of Intensive Care and Neonatology University Children's Hospital Zurich – Eleonore Foundation Steinwiesstrasse 75 CH-8032 Zurich phone +41 44 266 35 27 Cornelia.Hagmann@kispi.uzh.ch
Study Center	University Children's Hospital Zurich – Eleonore Foundation Steinwiesstrasse 75 CH-8032 Zurich
Data privacy	Data generation, transmission, storage and analysis of health related personal data and the storage of biological samples within this project will strictly follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5.
Ethical consideration	The strength of this study design is that the intervention is non-pharmacological, individualized, family-integrating and relation-based, builds a bridge between hospital

	and home care, and has a relevant primary outcome measure which if improved has long-lasting beneficial effects on both parental and infant outcome. Improvement of parent-infant interaction will have a great impact on child regulatory abilities, behaviour and ultimately long-term cognitive functions, and this in a high-risk population for later deficits in higher cognitive functions and behaviour and parents with known high burden of parental mental health problems. This music intervention will be easily implementable into clinical routine, and it will be translational for other population at risk such as for example infants and parents with gastrointestinal or visible malformation. Furthermore, it will be applicable in low- and high resource settings.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

Congenital heart disease (CHD) is the most common birth defect, with a rate of 8 per 1000 live births. Children with CHD are at increased risk for motor, cognitive and behavioral impairments from early childhood onwards through adolescence into adulthood [1] and therefore CHD is classified as a chronic disease. Infants with CHD require neonatal intensive medical and nursing care during several weeks. High levels of **stress and distress** experienced by mothers and fathers are the result of their infant's cardiac diagnosis and hospitalization, particularly in the perioperative phase [2-5]. For parents of infants with CHD (PCHD), the highly technological intensive care unit environment is foreign and frightening: the appearance of their child in the intensive care unit and the medical equipment/noise/light is stressful, expressions such as real life in the NICU is a "roller coaster", feeling scared that my child could get very sick or die, fear of their infant suffering, feeling helpless over their child condition, were not able to help or protect their child, are common. In addition, PCHD experience an altered parental role which disrupts the sense of self as a parent [2, 6-11]. Infants may be immediately separated from their parents after birth, causing an alteration in the normal bonding and attachment process [8].

Parental stress and mental health are becoming recognized as an important factor that influences child health and neurodevelopmental outcomes. In a large Norwegian birth cohort early parental PTSD symptoms measured at 8 weeks postpartum had an impact on social-emotional development at two years of age even after adjustment for confounders such as maternal mental health [12]. In the CHD population, higher parental stress is associated with lower cognitive scores [13]. And parents who report higher parent and child-related stress, at both 1 and 4 years, reported more child behaviour problems at age 4 years [14]. Other studies support similar associations between parental mental health and neurodevelopmental outcome of CHD children [10, 15]. Maternal mental health, maternal worry, cyanotic status and parenting style accounted for 95% of the variance in behavioural outcome highlighting the importance on intervention based on family factors, strengthening the evidence that parental mental health might more strongly predict child behavioural adjustment than other physiologic or surgical factors [10].

CHD Parent-Infant relationship

Infants with CHD require neonatal intensive medical and nursing care from birth onwards to the age of several weeks, during a critical phase of brain development and parental-infant interactions (bonding, attachment). Adverse early experience or stressful early environment can impair the self-regulatory capacity of these infants. Hence, these infants often show inconsistent behavioural cues, for example with feeding [16], they seem more difficult to soothe than healthy infants, especially those with single ventricle physiology [17] and are at high risk for problems with social, emotional, and behavioural regulation in childhood [18] and adolescents [19]. Indeed, increased

risk of feeding, motor and self-regulatory difficulties during early infancy give way to later emerging deficits in attention, executive function, visual-spatial processing, and social cognitive capacities during childhood and adolescence [20]. In a qualitative interview study with 91 mothers, the impact of CHD on mothers had four main themes: 37% said they had difficulties to have an *emotional tie*, 23% reported *bonding difficulties*, 19% mentioned *anxiety and worry* about their infants and 11% *caregiving behaviours* toward their infant [21]. Due to psychological stress mothers of CHD report difficulties in establishing mother-infant bonding, particularly also in relation to the feeding process [22]. This might also result from a bi-directional effect between mothers and children partly explained by high level of maternal distress being associated with infant's social withdrawal [23].

Only a few studies have focused on the attachment and bonding process between parents and infants with CHD. In 1991, Goldberg et al. indicated that significantly fewer infants with CHD, in comparison with healthy peers, were considered to have secure relationships with their mothers [24], interestingly the severity of illness did not have a direct impact on the quality of the infant-mother relationship in that study. Gardner et al. showed less positive affect and engagement in CHD infants than in the non-cardiac infants [25]. Lobo et al. reported mothers of CHD scoring lower on mother-infant interaction during feeding [26]. One study examined specifically the experiences of fathers showing that less positive behaviour towards the infant was observed in fathers with high level of stress in relation with handling the infant's difficulties, parental competence and connection to their infant. More recently, maternal-infant interaction was analysed in 16 healthy infants and in 15 infants with transposition of the great arteries at two weeks of age [16]: a video during feeding was recorded and analysed according the Parent-Child Early Relational Assessment [27]. No significant differences could be found in the dyadic interaction between the two groups [16]. This might be explained by the fact that only infants with transposition of the great arteries with a known high survival rate and low rate of morbidity were included and because of the early timing of mother-infant interaction assessment, namely two weeks of age whereas previous publications assessed mother-infant interaction much later.

It is thought that the formation of a strong bond between a mother and her infant can lead to more positive parenting behaviours and improved cognitive and neurobehavioral development of a child [28], while failure to establish this bond during infancy can have serious long-term effects on the mother-child relationship, affecting the child's development [29, 30]. Indeed, bonding and early social experiences are assumed to be associated with a more healthy social and emotional development, to protect against stress and make children more resilient [30, 31]. Le Bas et al. reports on the influence of mother's self-reported bond on the child's social and emotional development showing that better maternal-infant bonding was associated with higher socio-emotional scores at two years of age [30]. Joas et al. showed in a longitudinal study of a community sample, that less optimal maternal bonding measured at 6 weeks postnatally predicted lower social competencies at 5.5. years of age [32] suggesting an early influence of maternal bonding on children's social skills in preschool age.

Neonates who spend days or weeks in the neonatal and cardiac intensive care unit during a period of critical brain development suffer in the short term and long term as a result of their environmental exposures and impaired parental attachment.

Oxytocin and parent-infant interaction

The neuropeptide oxytocin (OXT) has been shown to play a key role in processes of parent-infant bonding [33]. Oxytocin arguably stimulates maternal feelings, influences maternal behavior, promotes bonding and at the same time is itself derived from early social interaction [32, 34, 35]. Many studies suggest that regulation of the OXT system mediates the negative effects of an atypical early social environment (such as early maternal separation), and promotes pro-social

behaviors [36]. In particular, during the early period after birth, OXT regulates maternal behaviors by promotion of social interactions and positive emotions [37]. Feldman et al. showed systematic increases in OXT in response to maternal highly affectionate contact suggesting that interventions to improve maternal-infant bonding should focus on increasing the mother's affectionate contact [33] as for example with music intervention. Interestingly, in fathers, highly stimulatory rather than affectionate contact appeared to have a greater impact on fathers and the post-contact assessment showed higher OXT in fathers compared to mothers [33]. They concluded that it is possible that whereas hormones associated with birth, lactation, and affectionate contact may induce hormonal changes in mothers, tactile stimulation and active forms of behavior such as exploration may shape the neuroendocrine basis of fatherhood [33]. Studies suggest that parental exposure to infant cues, particularly those of one's own infant, are associated with changes in the parent's hormonal profiles as well as activation in brain regions associated with reward and attachment [38, 39].

Evidence of interventions for parental mental health

In 2019, a systematic review of all relevant, available evidence derived from controlled trials was conducted to inform best practice principles for the mental health care of parents and their infants with CHD during intensive care unit admission [2]. First important finding was that this review revealed an extremely limited evidence base [2]: only five interventional trials, of these only two RCTs, could be included. All interventions were delivered face-to face bedside and the interventions varied considerably in therapeutic orientation, content, format, process, duration, dose and interventionist [2]. This review reports partial support for example in reducing maternal anxiety, improving maternal-infant attachment, parenting satisfaction as well as infant mental development at six months. However, these results derived from these trials must be interpreted with caution, due to high or serious risk of bias [2]. These studies highlight the importance of the research and support of parental mental health in order to support the parent-infant relationship and childhood outcome in infants with congenital heart disease [13].
Indeed, the conclusion of this systematic review is clearly that interventions for parents of infants with complex CHD (or any congenital anomaly) are in the early stages of research and that existing studies are predominantly pilot in nature, rather than randomized controlled trials of intervention efficacy. Furthermore, it was noted, that fathers were almost never included in these trials, with only one of the five trials reporting on paternal outcome data.

Music intervention on NICU

In neonatal medicine, music therapy is a triadic relationship between the parents, the infants and the music therapist, which serve as a source of respite or direct support of the parents [40]. **Individualized** and **family-integrating music therapy** approaches that incorporate parental involvement is called "**creative music therapy**" (CMT). CMT is an individualized, resource- and needs-oriented music therapy approach that is based upon the principles by Nordoff and Robbins [41] and further adapted to the needs of preterm infants by Haslbeck [42]. The music therapist establishes human contact with the newborn infant through improvised, entrained infant-directed humming. The music is tailored continuously to the affects, rhythms, and needs of the infants; hence individual needs, responsiveness and communicative musicality are some of the principles of CMT. CMT aims to relax the infant as well as to offer individualized interaction, meaningful stimulation, and entrained rhythms [42]. The parents are involved individually in the therapeutic process, e.g., by supporting them in singing to their infant and fostering an intuitive parent- infant interaction, so as to strengthen the bonding process [42, 43]. CMT aims to promote parental self-confidence, competence and autonomy and enhances the parent-infant bonding process [42].

Music interventions in term infants

Most of the evidence on music intervention on NICU is derived from studies in preterm infants with very few RCT on music intervention in healthy or high-risk term infants. Shoemark et al. has

discussed the markers of interplay between music therapist and the high-risk full term infant [44]. She was looking at whether the medically fragile term born infants use the same behavioural cues as their preterm counterparts giving important insight as to whether the music intervention developed for preterm infants must be adapted when applied to high-risk full-term infants. Robust evidence on the effect of music therapy on high-risk term infants or on parental mental health, let alone on parent-infant interaction are lacking. **Assessing the parent-infant relationship in high-risk term newborn infants is one of the main research gaps, with an even larger gap in evidence-based interventions to improve parent-infant interactions and child outcome.**

Transition to home
Discharge from the NICU indicates that the infant is no longer in medical danger. On the one hand, parents may feel relief, as their infant is no longer in danger and can return to a safe and familiar environment, but, on the other hand, there is increased parental stress and anxiety due to the new situation [45]. Parents become responsible for carrying out procedures such as providing medications and developmental care, which are services that were previously provided by supportive healthcare professionals in a medical environment. Furthermore, PCHD continue to have worries and anxiety about their child's survival and long-term outcome. Hence, NICU discharge dyads are in a vulnerable situation. There are only a few MT studies in preterm infants that addressed NICU discharge dyads [45-47] of which some have shown that MT after discharge empowered the mother's competence to interact with her infant and led to a gain in parental efficacy [45, 46].

What would be the rationale to use CMT in the CHD population? Infants born preterm and born with CHD both experience critical illness early in life, are hospitalised for many weeks, and subsequently, are both at high risk for long-term developmental and behavioural impairments. At preschool age, children with complex CHD and children born very preterm share an overall risk for neurodevelopmental deficits (own data, Wehrle et al., under revision). This seems persistent into adolescence: adolescents born with CHD and adolescents born preterm have similar cognitive, motor and behavioural outcomes. Also, parental mental health problems and altered parent-infant interaction are present in both, the preterm [48, 49]; and CHD population [50], with a larger burden in the parents of CHD infants. This led to the hypothesis that CMT might have a beneficial impact on PCHD and infants, more specifically, CMT might improve parent-infant interaction and parental mental health in PCHD, and ultimately, most importantly, in the child's outcomes. However, as CMT has mainly been applied in preterm infants, and not in high-risk term infants such as infants with CHD, we will as a first step, perform a qualitative mixed-method study, to tailor and adapt the preterm CMT intervention protocol to our high-risk population, and then perform a RCT to prove the efficacy of CMT on parent-infant interaction.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

The main aim of this interventional randomized trial is to evaluate if parent-infant interaction can be improved by a standardised, **family integrated, individualized, interactive resource- and needs-oriented MT approach** in the dyads of infants with CHD and their parents.
Aim 1: to evaluate if the previously published clinical practice CMT protocol for preterm infants [51] can be applied to term born infants with CHD and PCHD.
Aim 2: to conduct a pragmatic interventional RCT to evaluate the efficacy of CMT on parent-infant-interaction, parental mental health and child's outcome:

1. Will CMT improve **mother-infant interaction** assessed at child age 6 months?

a. Mothers in the interventional arm will have more positive affective involvement, verbalization, and mirroring than mothers in the control arm (P1 PCERA).
b. Better postnatal attachment and bonding will be found in mothers in the interventional arm than in mothers in the control arm (MPAS, PRAM, PBQ).
c. Better dyadic mutual enjoyment/ reciprocity and less dyadic disorganization/ tension will be found in the mother-infant dyad in the interventional arm.

2. Will CMT improve **parental mental health?**
   a. Mothers and fathers in the interventional arm will have less parental stress (PSS-10, PSS:NICU) at discharge and at child age 6 months than parents in the control group (PSS-10).
   b. Mothers and fathers in the interventional arm will have less state anxiety (STAI) at discharge and at child age 6 months than the parents in the control group.
   c. Mothers and fathers in the interventional arm will have fewer clinically relevant depressive symptoms (EPDS, PH-Q9) at discharge and at child age 6 months than the parents in the control group.
   d. Mothers and fathers in the interventional arm will have fewer clinically relevant symptoms of posttraumatic stress disorder (PDS) at discharge and at child age 6 months than the parents in the control group.
   e. Mothers and fathers in the interventional arm will have less negative affect and behaviour and less intrusiveness, insensitivity, and inconsistency (P2-3 PCERA).
3. Will early **child outcome** be improved by CMT?
   a. Functional and structural connectivity will be better in infants in the interventional arm compared to infants in the control group, irrespective of brain injuries.
   b. Infants in the interventional group will have better affect, social and communicative competence, less irritability and less dysregulation (I4-6 PCERA).
   c. Infants in the interventional arm will have better regulatory abilities than infant in the control arm, independent of severity of the congenital heart disease (IBQ-R, SFS).

3.2 Primary and secondary endpoints

Mother-infant interaction

The primary endpoint is mother-infant interaction measured at 6 months of age. As most evidence on parent-infant interaction is based on mother-infant interaction, we will use the video of a mother-infant interaction as the primary outcome. In PCERA, the subscale P1 "Parental Positive Affective Involvement and Verbalisation" is chosen for primary outcome assessment for its high internal consistency and reliability and its correlation with the attachment subscales of the Parent stress Index [27]. The feeding sequence was chosen because feeding problems are frequent, require good regulatory abilities and maternal adaptive behaviour [16, 26].

Parental mental health

For parental mental health assessment the endpoint represents the questionnaires listed in the Table 1.

Secondary endpoints for **Infant outcome** assessed by
- Brain Magnetic resonance imaging
- The Infant Behavior Questionnaire Revised (IBQ-R), Infant Temperament
- Fragebogen zum Schreien, Füttern und Schlafen

3.3 Study design

This is a pragmatic, interventional, single-center randomized controlled clinical trial conducted in newborn infants with congenital heart disease and their families. Infants admitted to our PICU/NICU and eligible for the study, will be recruited after parental consent. Allocation to the interventional arm (music therapy) or standard of care (control) will be randomized 1:1. Block randomization will be employed with stratification by risk of CHD ("low risk" vs "high risk") according to the Risk Stratification for Congenital Heart Surgery (RACHS-2) tool [52]. This will ensure a good balance of risk of CHD between treatment groups. Randomization will be done in RedCap by the study coordinators and supervised by the local representative of the SwissPedNet. The randomization will be computer-centralized and concealment of allocation is guaranteed.

By combining integrative approaches, the effects of the music therapy will be evaluated on:
- The parent-infant interaction
- The parental mental health
- The early child outcome

Blinding: Due to the nature of the intervention, blinding of the intervention is not possible; however, all outcome assessors such as for example the video raters, the statistician, the MR Analysist etc. will be blinded to the group allocation. They will not be in contact with the parents or study coordinators which will be responsible for randomization.

3.4. Study intervention

Intervention: CMT has been previously applied in our randomized controlled pilot trial [53, 54], a clinical practice protocol has been published [51] and a framework for music therapy with premature and newborn infants and their parents in German- speaking countries and Switzerland has been developed by the Fachkreis Musiktherapie Neonatologie (FMtN) (https://www.musiktherapie.de/wp-content/uploads/2019/05/Referenzrahmen-Fachkreis-Musiktherapie-Neonatologie.pdf). The specific interventional CMT protocol is derived from specific aim 1. Within CMT, a certified, well-trained and experienced music therapist will formulate an individualized, culturally adapted treatment plan based on an initial infant–parent assessment, which includes assessment of parental needs, musical heritage, culture, context, and parental integration in the therapeutic process [42]. CMT aims to honor the family's musical and cultural heritage and to integrate their favorite music or song to empower the family in their cultural identity [40, 42]. During a MT session, the music will be adapted continuously to the affects, rhythms, and needs of the infants. The family is integrated individually in the therapeutic process [42]. CMT frequency per week and length per session during hospitalisation and after discharge will be defined in the mixed method study. Each infant will receive at least 10 CMT interventions during hospitalization until discharge. After each session, the fidelity checklist will be completed by the music therapist. All music therapists will be certified music therapist and trained accordingly by Haslbeck. *Fidelity of the intervention:* we will measure fidelity to confirm that the intervention is delivered as it was designed and to ensure that the intervention was consistent over time so that the results then can be accurately attributed to the intervention [55]. The CMT is done according to a predefined interventional MT protocol and based on this standardized protocol we will develop a fidelity checklist. During the implementation phase of the trial, we will pilot-test the final process checklist with two raters observing and rating three sessions each. We will define core process scores which will be consistent with a good intervention and to have high inter-rater reliability [55]. During the total period of the interventions, the interventions to be rated will be randomly selected, the interventions will be videotaped and rated at a later time point by two trained raters. Cohen's kappa will be calculated. For the process scores, interclass-coefficients will be calculated for each point of the final process list [55]. On an organizational level, we will

recruit certified music therapist with similar level of experience, they will receive the same amount of study training (training fidelity) and we will record the case load of each therapist. To ensure treatment fidelity, our study coordinator oversees regularly scheduled checks of both our outcome assessors and our intervention therapists.

Control group: Infants allocated to the control group will receive standard care during admission. Standard care includes involvement of a multi-professional team consisting of medical and nursing team, psychologists/psychiatrists, social workers, breastfeeding counsellor, speech therapist, nutritional counsellor and physiotherapists.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Project population, inclusion and exclusion criteria

Inclusion criteria

Eligible for this study are all newborn infants with CHD born >35 weeks of gestational and <28 days at diagnosis of CHD irrespective of severity of the heart disease and admitted to NICU/PICU at the Children's University Hospital Zurich. Infants with syndromes and /or confirmed chromosomal abnormalities will also be included.

Exclusion criteria

Patients with a gestational age at birth <35 weeks, or age >28 days at diagnosis of CHD will not be included in the study. Moreover, only study participants with written informed consent of the parents / legal guardians will be recruited into the study.

4.2 Recruitment, screening and informed consent procedure

The study coordinator team will screen each day all infants admitted to the neonatal and pediatric intensive care units at the University Children's Hospital Zurich for eligibility. If eligible, the principal investigator and the study coordinator team will get in contact with the parents of the child. The investigators will explain to the parents the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. The parents will be informed that the participation in the study is voluntary and that they may withdraw from the study at any time. Withdrawal of consent will not affect subsequent medical assistance and treatment of their child.
The parents will be informed that the medical records of their child may be examined by authorised individuals other than their treating physician.

All parents will be provided with a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Within the first week of admission of the child on the NICU/PICU, the parents will have time to decide whether to participate at the study or not.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The consent form will be signed and dated by the investigator or his designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records.

4.3 Study procedures

The planned overall study duration is about 4 years, with recruitment start in July 2022 and end in 2025. Since final assessment of primary outcome will be 6 months later, publication of the primary outcome is planned for 2026.

A schematic overview of the study is showed in Figure 1. At three different time points (T1: pre-intervention baseline, T2: at discharge, T3: at 6 month of age) primary and secondary outcomes will be measured via standardised questionnaires, laboratory analysis, or video records (Table 1).

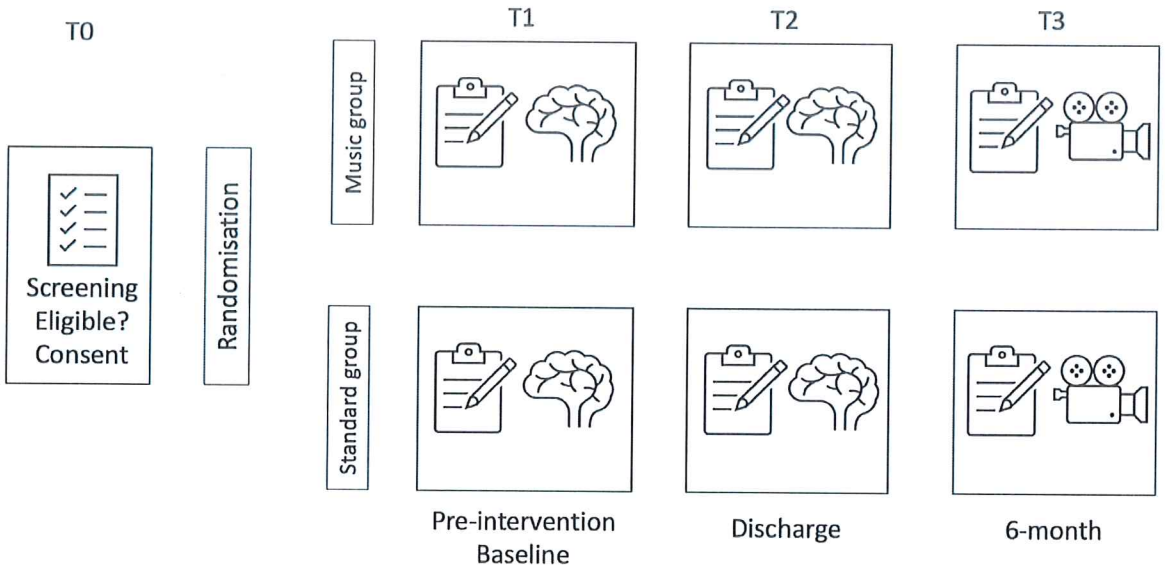

Figure 1. Schematic overview of the trial. At time point 0 (T0) patient will be screened for eligibility and consent will be asked to the parents. Randomization into the two study arms (Intervention: music group; Control: Standard group) will be conducted via RedCap. Parent-infant interactions as well as parental mental health will be assessed via standardized questionnaires and Oxytocin measurements (time points T1 and T2). A video record of a feeding session will be performed at time point 3 (T3).

Table 1: Overview of all measured outcomes.

	Parental Outcomes			
	T1 (baseline)	T2 (discharge)	T3 (6 months)	Duration (min)
Primary outcome				
Mother infant interaction, PCERA P1			x	30
Secondary outcome measures ***(both fathers and mothers complete questionnaires)***				
Parent-infant interaction				
Items	T1	T2	T3	
Maternal postnatal attachment scale (MPAS)	x	x	x	10
Postpartum Bonding Questionnaire (PBQ)	x	x	x	15
Pictorial Representation of Attachment Measure	x	x	x	10
Saliva Oxytocin (before/after CMT intervention)		x		
Parental mental health				
Items	T1	T2	T3	
General health (GHQ-12)	x	x	x	10
Patient Health Questionnaire (PH-Q9)	x	x	x	5
Edinburgh Postnatal Depression Scale (EPDS)	x	x	x	10
Spielberger State Anxiety Scale (STAI)	x	x	x	10
Perceived Stress Scale (PSS-10)	x	x	x	5
Parental stress scale (PSS:NICU)	x	x	x	10
Post traumatic diagnostic scale DSM-5 (PDS)	x	x	x	15
Other outcome measures				
Paternal-infant interaction and protective factors				
Items	T1	T2	T3	
Paternal-infant interaction PCERA			x	
Baseline Music questionnaire	x			10
F-Soz U Social Support Questionnaire	x		x	5
SES	x			5
Resilience Scale 13	x		x	10
Big five inventory-10	x			10
Infant secondary outcome measures				
Items	T1	T2	T3	
Brain Magnetic resonance imaging	x	x		45
The Infant Behavior Questionnaire Revised (IBQ-R), Infant Temperament			x	15
Fragebogen zum Schreien, Füttern und Schlafen			x	15

4.3.1 Video Records

Mother-infant interaction:

For the primary outcome, mother infant interaction will be measured at 6 months of age. Mothers will be filmed during a feeding session with their infant. They will be instructed to feed the infants in the manner in which they usually feed (breast or bottle-feed) in a room at home where feedings routinely occurred; the first 5min of the feeding will be coded using the PCERA [27]. As most evidence on parent-infant interaction is based on mother-infant interaction, we will use the video of a mother-infant interaction as the primary outcome. In PCERA, the subscale P1 "Parental Positive Affective Involvement and Verbalisation" is chosen for primary outcome assessment for its high internal consistency and reliability [27] and its correlation with the attachment subscales of the Parent stress Index [27]. The feeding sequence was chosen because feeding problems are frequent, require good regulatory abilities and maternal adaptive behavior [16, 26].

Parent-child infant interaction

Video recording [27]: three sequences of parent-child interactions (during free play, feeding, or a structured task) will be videotaped at the homes of the families. Both, fathers and mothers will be filmed. The recording will be conducted by the music therapist and/or study coordinator and later coded by trained raters blinded to group allocation. The PCERA is a well-established measure to assess parent-child interaction during early development.

The PCERA has previously been used to describe mother-infant interaction in preterm infants [48, 49, 56] and in one study in infants with transposition of the great arteries (TGA) [16]. The PCERA assesses the parent's positive affective involvement, verbalization, and mirroring (P1); negative affect and behavior (P2), and intrusiveness, insensitivity/inconsistency (P3) [27]. PCERA examines also the infant's positive affect, social and communicative competence (I3); the infants' play, capacity for interest and attentional skills (I5), and dysregulation and irritability (I5). Last, the PCERA assesses mutual enjoyment and reciprocity (D7), as well as tension or disorganization of the dyad (D8) [27]. There are in total 8 scales derived of all items, three parental there infant and two dyadic scales [27]. The variables/items in each scale are averaged together to form a total score between 1 and 5 [27]. Previous studies have found that the PCERA has an acceptable range of internal consistency, factor validity [27] and discriminate validity between high risk and well-functioning mothers [57]. Each variable/item is coded on a 5-point Likert-type scale with a 1 (less positive and/or more negative affect or behavior) to 5 (more positive and/or less negative affect or behavior) scale. Anchor points are defined as for each point on every variable with: 1 to 2 defined as an area of concern; 3 as an area of some concern and 4 to 5 as an area of strength. Coding of the videos will be done later by trained PCERA raters: they are trained to reliability and will be blinded to the group allocation. They will not be in contact with any of the unblinded parents. Training of raters will include 40 hours of training and rated pilot tapes during the training period [27, 49, 56]. Intra-and inter-observer agreement will be evaluated. The coding of the videos will be done by the PhD student and the study coordinator which will be blinded to the group allocations.

4.3.2 Questionnaires

Parental mental health:

General health (GHQ-12) [58]: The 12-Item General Health Questionnaire (GHQ-12) consists of 12 items, each one assessing the severity of a psychological distress over the past few weeks using a 4-point Likert-type scale.

Patient Health Questionnaire (PH-Q9) [59]: The Patient Health Questionnaire is a self-administered version of the PRIME-MD diagnostic instrument to screen for depression. It must be recalled how often certain symptoms have been experienced over the last two weeks.

Edinburgh Postnatal Depression Scale (EPDS) [60]: The EPDS is the most common 10-item scale questionnaire that has been developed to measure mother's postpartum depression symptoms, parents are asked to respond to ten items on a four-point Liker. It was also shown to be useful for measuring father's postnatal depression by several studies [61].

Spielberger State Anxiety Scale (STAI) [62]: The STAI is widely used a 40-item self-report scale that assesses separate dimensions of "state" and "trait" anxiety. The state measurement assesses how the individual feels "right now" or at this moment. The trait anxiety measure addresses how the individuals generally. The rating is done on a four-point Likert scale.

Perceived Stress Scale (PSS-10) [63]: The 10 questions Perceived Stress Scale is widely used to measure self-reported stress. The questions will be answered on a five-point scale from 'never' to 'very often' and a total PSS score can be calculated by summing across all items.

Parental Stressor Scale (PSS-NICU) [64]: the German version of the scale consists of 13 items and assesses the extent of stress caused by experiences in the ICU. It comprises two subscales: infant behavior and appearance, and parental role alterations. Responses are given on a five-point scale ranging from 1 to 5.

Post traumatic diagnostic scale DSM-5 (PDS) [65]: The PDS is a very commonly used 17-item self-report instrument that rates symptoms of PTSD according to their frequency on a 4-point scale from 0 (not at all) to 3 (almost always).

Parent-child infant interaction

The Maternal Post-Natal Attachment Scale (MPAS) [66]: this widely used questionnaire contains 19 items measuring maternal feelings toward the infant. All items are rated with a score of 1 (low bonding) to 5 (high bonding), with higher scores indicating higher feelings of attachment toward the infant. The sum of the 19 items forms the total MPAS scale. The MPAS is composed of three scales: (1) Quality of attachment, (2) Absence of hostility and (3) Pleasure in interaction.

Postpartum Bonding Questionnaire (PBQ) [29]: PBQ is a self-report screening measure of difficulties in the maternal-infant relationship and has been validated in the sample of mothers with different forms of maternal-infant disorders. The PBQ has 25 items rated on a 6-point scale (0—never to 5—always), with several reversely scored items, where a higher score indicates more disturbed bonding. Four subscales measure General Factor (12 items), Rejection and pathological anger (7 items), Anxiety about infant (4 items), and Incipient abuse (2 items).

Pictorial Representation of Attachment Measure (PRAM) [67]: this is a measure to assess the nonverbal representation of antenatal attachment or bonding between parents and their child. The PRAM has proven to be a valid and easy-to-administer tool to assess parental bonding processes [68]. The PRAM provides a visual representation of the relationship between the parent and their child. In our recently published pilot study on creative music therapy in preterm infants, the PRAM has proven to be useful to assess attachment [69].

Protective factors

Baseline music questionnaire (GEMUBAQ) [70]: This is a questionnaire in which the parents are asked about a number of musical activities and how much they perform these activities. This serves as a baseline to evaluate the parental background and attitude toward music.

F-SozU Questionnaire [71]: a widely used German self-report 22-item questionnaire will be applied for the assessment of social support. The answers are based on a 5 Likert scale. The global scale and the four major scales (emotional support, instrumental support, social integration, and social strain) show high values of internal consistency (Cronbach alpha between .81 and .93) [71]

Socioeconomic status (SES) [72]: the parents will complete a questionnaire which assesses their education, their occupation and their salary. SES is calculated according to Largo et al. [72] by means of a six-point score of both maternal education and paternal occupation. The lowest possible SES score for either the mother or the father is 1, the highest 6. The overall SES score is a simple addition of the 2 individual scores resulting in a value between 2 and 12.

Resilience Scale 13 (RS13) [73]: RS13 is a self-assessment procedure to assess coping ability in terms of personal competence and individual resilience. This scale includes central aspects of resilience, such as emotional stability, joie de vivre, energy, openness to new things, optimism, and the ability to change perspective. A seven-point Likert scale forms the response options from 1="No, not true" to 7="Yes, exactly true".

Big Five Inventory-10 (BFI-10) [74]: The BFI-10 is a 10-item scale measuring the Big Five personality traits Extraversion, Agreeableness, Conscientiousness, Emotional Stability, and Openness.

Infant secondary outcome measures

The Infant Behavior Questionnaire Revised (IBQ-R), Infant Temperament [75]: this is a well-established caregiver report measure of temperament for infants aged 3 to 12 months. This instrument assesses 6 domains of infant temperament (activity level, soothability, fear, distress to limitations, smiling and laughter, and duration of orienting). It consists of 91 items and 14 scales. Parents are asked to report, on a 7-point scale, the frequency with which infants have showed specific behaviors in common situations during the past week or 2 weeks.

Fragebogen zum Schreien, Füttern und Schlafen (SFS) [76]: the SFS gives an overview of the child behavior regulation and the associated difficulties within the frame of parental assessments. Duration of crying, length of sleep, distractibility, dysfunctional communication patterns in calming strategies, bedtime rituals, feeding procedures and interpretations and explanations for the parents' problem, own burden will be evaluated.

4.3.3 Laboratory analysis and magnetic resonance imaging

Saliva Oxytocin: we are interested in evaluating the immediate effect of CMT on the Oxytocin levels. Four measurements will be done in mothers/ fathers/ newborn infants immediate before/after CMT: first, when CMT is done during skin-to skin care, 2nd when CMT is done while the infant is in the bed, third measurement with both parents present during CMT, and the fourth measurement at the T3 [33]. Saliva will be collected into Cortisol-Salivettes (Sarstedt, Nürnbrecht, Germany) and further processed at the Center for Pediatric Laboratory Medicine of the University Children's Hospital Zurich. This results in general in 1 ml of saliva from one collection. Oxytocin will be measured with an ELISA assay from ibl International (Tecan, Männedorf, Switzerland). The measurements will be done in the afternoon in order not to confound the levels with diurnal changes [77].

Magnetic resonance imaging: neuroimaging of the newborn infants will be done at T1 and T2 to assess brain development itself and to evaluate the effect of CMT on brain development. In all infants, neuroimaging will be performed at T1 if the clinical condition of the infants allows it. We perform routinely in all infant with CHD a Brain MRI post-surgery before T2. Infants with CHD not requiring neonatal surgery will be scanned at T2 for research purposes only. We will acquire resting state functional MRI (functional connectivity), diffusion weighted and tensor imaging (structural connectomics), magnetic resonance spectroscopy (brain metabolism), arterial spin labeling (cerebral perfusion), multi-component T2 relaxometry (myelination).

4.4 Withdrawal and discontinuation

In case of withdrawal of informed consent, there will be no further study visits and sample collections. Already collected data and samples will be processed and analysed as outlined in chapter 5.3.

5 STATISTICS AND METHODOLOGY

5.1. Hypothesis and sample size calculation

Statistical methods and sample size estimation have been developed in collaboration with the senior statistician Dr. Stefanie von Felten from the Research Methods Consulting Unit of the University of Zurich, Epidemiology, Biostatistics and Prevention Institute, Biostatistics Department (EBPI). Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. The statistical analysis plan will be finalized before database closure and will be under version control at the Department of Biostatistics, University of Zurich.

The research hypothesis is, that music therapy will enhance Parental Positive Affective Involvement and Verbalisation, as measured by the P1 subscale of PCERA of the mother (primary outcome). The null hypothesis to be tested is that treatment groups do not differ with regard to the primary outcome, i.e., the mean difference is zero. The two-sided alternative hypothesis is that they do differ, i.e., the mean difference is not zero.

Sample size calculation

We expect a mean difference in the P1 subscore of PCERA between the intervention group and the control group of 0.5 points, based on an expected mean of 3.5 in the control group (approximately the overall average observed in healthy infants and infants with transposition of the great arteries by Harrison and Ferree [16] and an increase to 4.0 points with music therapy. We further expect a standard deviation of 1 point, which is slightly more than observed within groups by Harrison and Ferree [16]. To ensure a power of 80% at a significance level of 5 %, we will need a total of 130 evaluable patients. Considering a drop-out rate of 20 %, a total of 164 will need to be recruited. To assess the sensitivity of the sample size with regard to the expected mean difference and standard deviation, we conducted a series of power calculations using the R package sse [78], using the power and significance level specified above. A range of sample sizes ni=1,...,57 = 20, ..., 300 was considered, together with a range of mean differences (0.1–1) and a range of standard deviations (0.5–2). Sample size estimation was performed using the R system for statistical computing and graphics (R Core Team, 2021).

5.2. Planned analysis

5.2.1 Analised datasets and populations

The following data sets will be analysed:

- All patients randomized to the trial who survive until 6 months of age (all survivors set, ASS). We will exclude patients who died because we expect mortality to be independent of the trial intervention and thus to be similar in both groups. This set will be analysed according to the intention-to-treat principle, using multiple imputation of missing data.
- All patients in the ASS who completed the trial per protocol (per protocol set, PPS) and have a primary outcome measurement. Patients in the intervention group need to have a minimum of 10 music therapy sessions after hospital discharge to be included in the PPS. Should the received treatment differ from the randomized treatment in some cases, patients will be analysed according to the received treatment.

For the ASS and the PPS we will report baseline characteristics by trial arm. Mean and standard deviation will be reported for continuous variables with approximately normal distribution, median and inter-quartile range for ordinal variables or continuous variables with skewed distribution, and

frequency and percentage for categorical variables.

5.2.2 Primary analysis

The mean difference in P1 of the PCERA at 6 months will be estimated by a linear regression model with treatment group and risk of CHD (as used for stratification of the randomization) as explanatory variables. This analysis will be performed on the ASS. As sensitivity analyses, we will fit a linear regression model with SES as additional explanatory variable and one with treatment group as the only explanatory variable (unadjusted analysis). In addition, the analyses described above will be performed on the PPS. In addition to the mean differences on the original scale of P1 we will also estimate the corresponding Cohen's d as standardized effect size

5.2.3 Secondary analysis

For the secondary outcomes (measured on the mothers), unadjusted mean differences at 6 months follow-up will be estimated by linear models with treatment group as the only explanatory variable and adjusted mean differences will be estimated by linear models with risk of CHD and SES as additional explanatory variables. For "parental stress scale (PSS:NICU)", unadjusted and adjusted mean difference will be estimated at hospital discharge (as this outcome is not measured at 6 month follow-up). In addition, we will analyze the repeated measurements (at hospital discharge and after 6 months follow-up) by linear mixed-effects models with a random intercept per patient, and treatment group, visit (discharge or 6 months) and the group × visit interaction will be used as explanatory variables. All outcomes (primary and secondary) will also be analyzed descriptively, as described above for the baseline characteristics. Corresponding measurements on the fathers are expected to be less complete and will only be analyzed descriptively.

Exploratory subgroup analyses are planned with regard to the primary outcome for subgroup by SES, risk of CHD, gender and genetic and syndromic abnormalities. For each subgroup variable, a linear model will be fitted to the primary outcome with treatment group, the subgroup variable, and the interaction between treatment group and subgroup variable as explanatory variables. A statistically significant interaction between a subgroup variable and treatment group would indicate a different treatment effect in the corresponding subgroups (or along a gradient of SES or Risk of CHD). We will also estimate group-specific treatment effects (with 95 % CI), fitting a separate model for the corresponding subgroups, which will be reported together with the interaction p-value to assess the degree of standardization of the intervention, a fidelity analysis will be performed [137]. Handling of missing data and drop-outs: we will use multiple imputation by chained equations to be able to analyse the ASS. Complete case analyses will be used in addition.

To assess the degree of standardization of the intervention, a fidelity analysis will be performed [79].

5.3. Handling of missing data and drop-outs

We will use multiple imputation by chained equations to be able to analyse the all survivors set. Complete case analyses will be used in addition.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

Exemptions from expedited reporting may be possible if the SAE is either a clear result of the underlying disease or well-known. These are the SAEs which are exempted from expedited reporting: Death, sepsis, necrotising enterocolitis, extra corporal membrane oxygenation (ECMO), pneumatothorax, seizures, white matter injuries, stroke, intraventricular hemorrhage,

cerebral edema, chylothorax, renal failure, coagulation disorder, cholestasis, respiratory failure, cardiac failure.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

6.3 Periodic safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

6.4 Radiation

No radiation will be used in this study.

6.5 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

6.6 Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

6.7 Insurance

In the event of study-related damage or injuries, the liability of the University Children's Hospital Zurich provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

CHD is the most common birth defect affecting 8:100 live born children. Finding a non-pharmalogical, easy implementable, well accepted and sustainable intervention to improve parent-infant interaction, parental mental health and ultimately long-term cognitive outcome of these children, will have a great impact on long-term health-related quality of life and academic achievements of these children. This evidence will guide us to improve our clinical management of the infants and PCHD during hospitalisation and after discharge, not only in Switzerland but worldwide. This music intervention will be easily implementable into clinical routine, and it will be translational for other population at risk such as for example infants and parents with gastrointestinal or visible malformation. Furthermore, it will be applicable in low- and high resource settings.

7.2 Risk-benefit assessment

The study design does not entail serious risks for the infants and parents enrolled as the intervention which is creative music therapy does not entail any risks for the infants or the parents. On the contrary, physiologic stability are reported in systematic review on music interventions.

There is no immediate benefit to the study participant of the standard group. However, if CMT proves to be successful it will be easily implementable in clinical routine. This evidence will guide us in improving our clinical management of the infants and PCHD during hospitalization and after discharge

7.3 Rationale for the inclusion of vulnerable participants

Assessment of the parent-infant relationship in high-risk term newborns is one of the main research gaps, with an even larger gap in evidence-based interventions to improve parent-infant interactions and child outcome. An individualized, family-integrating music intervention approach such as CMT might improve parental mental health, parent-infant interaction, and child outcome in CHD.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Data generation, transmission, storage and analysis of health related personal data and the storage of biological samples within this project will strictly follow the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5.

The personal working on this project will be trained on all important project related aspects. For quality assurance the Ethics Committee may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

8.2 Data recording and source data

The study data will be recorded using an electronic Case Report Form (eCRF) such as Redcap®, provided by the University Children's Hospital Zurich. The data will be accessible only by the study team and will be password protected. The data will be backed-up every night. There will be regular storage of data as report in PDF format, to illustrate and restore the data acquisition process.

The Institute for Medical Informatics I4MI of the Bern University of Applied Sciences BFH will develop a smartphone app for the collection of the parents' daily musical activity (reading aloud, playing music, singing/playing music), which should enable the fastest possible collection. The app will offer a reminder function, as well as a graphical display of time spent, to motivate parents and provide feedback on the contribution made to the therapy. The data will be stored in the secure platform MIDATA, which meets the requirements of the Data Management Plan (FHIR format, FAIR principles), Data Protection and Human Research Act. MIDATA is registered with the Federal Data Protection and Information Commissioner (FDPIC) as a data collection under number 201800070 (https://www.datareg.admin.ch/search). The app will be available for both Android and iOS operating systems and published in the respective app store. Since the app is not intended for the public, use can be protected via a code known only to the research team. Onboarding will require each parent to register with MIDATA, accept the terms of use and participation in the study, and enter the child's study number. The research team will be able to export the data collected from parents through the MIDATA portal. The data will be exported in pseudonymized form.

All data from the video recording at six months age will be stored on a password secured server and only study staff will have access. The recordings will be stored for ten years.

8.3 Confidentiality and coding

Participant confidentiality will be ensured by utilizing identification code numbers to correspond to medical information in the computer files. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project.
Samples will be encoded and the code given and stored by the project leader. The code will not be transmitted to the researchers.
On the CRFs and other project specific documents, participants are only identified by a unique participant number. Any document linking the subject number to subject identifiers will be kept in a password protected Excel sheet with access limited to the project leader and the sub-investigator. If new findings/diagnosis related to individual participants of the study are found as a result of this project, the participant will be informed by the sub-investigator, as explained and consented in the informed consent of the study.
Study data, also uncoded, will be kept for further research if the parents gave consent on the corresponding consent form.

Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel at the division of Clinical Chemistry and Biochemistry of the University Children's Hospital Zurich.

8.4 Retention and destruction of study data and biological material

Project data: All study data will be archived for a minimum of 10 years after regular study termination at the University Children's Hospital Zurich. Any patient files and source data shall be archived for the longest possible period of time according to the feasibility of the investigational site.

Biological material: Saliva samples will be stored at the Division of Clinical Chemistry and

Biochemistry (after permission by the patients involved in the study) for a minimum of 5 years.

9 MONITORING AND REGISTRATION

Monitoring will be performed according to monitoring plan.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

This trial is currently being evaluated for funding by the Swiss National Science Fundation (SNSF). Support from the following foundations has already been obtained:

- Gaydoul music
- Refugium
- Herz Stiftung
- Mart Maria von Schlitz

Project results will be published by the project leader and participating investigators in a timely fashion, and ensuring open access to provide maximal benefit to the medical and research community.

All principal investigators and other contributors are eligible for authorship. All authors of a manuscript need to fulfil the following criteria according to the guidelines of the International Committee of Medical Journal Editors (http://www.icmje.org/): 1. Substantial contribution to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, AND 2. Drafting the work or revising it critically for important intellectual content, AND 3. Final approval of the version to be published, AND 4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part or the work are appropriately investigated and resolved.

There is no conflict of interest.

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