Heart Rate Variability Biofeedback (HRVB) With Mothers Who Delivered a Preterm Infant: A Feasibility Study

NCT03565874

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Clinical Protocol template for Investigator initiated trials (IIT)

Clinical Study Protocol

Heart rate variability biofeedback (HRVB) with mothers having a preterm infant: A feasibility study

Short title: Heart rate variability biofeedback and prematurity

Study Type:	Other clinical trial
Study Categorisation:	Risk category according to LHR (A)
Study Registration:	Clinicaltrials.gov and Kofam.ch
Study Identifier:	2017-02199
Sponsor:	Prof. Kerstin von Plessen
Principal Investigator:	Sébastien Urben
Investigational Product:	Heart rate variability biofeedback

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ABBREVIATIONS

Provide a list of abbreviations used on the protocol - to be completed

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin)*
GCP	Good Clinical Practice
Ho	Null hypothesis
H1	Alternative hypothesis
HF	High Frequency
HRA	Federal Act on Research involving Human Beings
HR	Heart Rate
HRV	Heart Rate Variability
HRVB	Heart Rate Variability Biofeedback
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)*
LRH	Loi fédérale relative à la recherche sur l'être humain
MD	Medical Device
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain *(in German : KlinV, in English : ClinO)*
PI	Principal Investigator
RMSDD	Root-mean square differences of ssuccessive R-R intervals
RSA	Respiratory sinus arrhythmia

STUDY SCHEDULE

Study Periods	Screening	Treatment, Intervention Period		
Visit		Pre	Middle	Post
Time in days postnatal	3 ± 2	7	14 ± 3	21 ± 3
Patient Information and Informed Consent	x			
Demographics	x			
Medical History	x			
In- /Exclusion Criteria	x	x		
Medical Device		x	x	x
Primary outcomes: acceptability of the protocol, acceptability of the intervention, compliance, satisfaction with the intervention.				x
Secondary outcomes: heart rate variability, perceived stress, anxiety, depression.		x		x
Concomitant Therapy		x	x	x
Adverse Events		x	x	x

1. ETHICAL AND REGULATORY ASPECTS

The decision of the Competent Ethics Committee (CEC) concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

1.1 Study registration

The study will be registered on two database: an international one (www.clinicaltrials.gov) and a national one (www.kofam.ch).

1.2 Categorization of study

This feasibility study conforms to a clinical trial of medical devices under Category A as the medical device bears a conformity marking and it is used in accordance with the instructions.

1.3 Competent Ethics Committee (CEC)

The responsible investigator ensures that approval from an appropriately constituted CEC is sought for the clinical study. Duties and allowed time frame (all changes in the research activity and all unanticipated problems involving risks to humans; including in case of planned or premature study end and the final report) will be reported. No changes will be made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants. Premature study end or interruption of the study will be reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

1.4 Competent Authorities (CA)

Not applicable

1.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

Add other local requirements in case of medical device or international studies.

1.6 Declaration of interest

No conflict of interest to declare

1.7 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that she may withdraw from the study at any time and that withdrawal of consent will not affect her subsequent medical assistance and treatment. The participant must be informed that her medical records may be examined by authorized individuals other than their treating physician. All participants for the study will be provided 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. One day will be given to the participants to decide whether to participate or not. The patient information sheet and the consent form will be submitted to the CEC (submitted separately) to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

1.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator) or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

1.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention.

1.10 Protocol amendments

Substantial amendments are only implemented after approval of the CEC respectively. 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 sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

2. BACKGROUND AND RATIONALE

2.1 Background and Rationale

Preterm birth and stress

Preterm births (<37 weeks of gestational age) constitute a public health issue as they compromise children's developmental outcomes (Behrman & Butler, 2007; Sansavini et al., 2011). A growing number of preterm births (Brady et al., 2006) is observed, alongside with higher survival rates (Fanaroff et al., 2007). In Switzerland, preterm births referred to 7.1% of all live births (N=86'559) in 2016 (OFS, 2016). Preterm born children's vulnerability and uncertainty about future development often lead to psychological distress and anxiety in their parents, particularly in mothers (Holditch-Davis et al., 2009). Furthermore, such adverse experience is reported to lead to posttraumatic stress symptoms (i.e., re-experiencing of the traumatic event, avoidance of reminders, negative cognitions and mood, and hyperarousal) and to other mental health problems (Treyvaud et al., 2010). For instance, 40% of mothers of preterm children experienced post-traumatic symptoms at 6 months of infant corrected age (Holditch-Davis et al., 2003) and 26% still experience post-traumatic symptoms at 18 months of infants corrected age (Pierrehumbert et al., 2003). Taken together, these results suggest that a preterm delivery is an adverse life event putting mothers at risk for psychological distress.

Physiological aspects of stress

A widely recognized model apprehending the stress phenomenon is the "allostatic load model" (McEwen, 1998). Allostasis refers to dynamic responses aiming at maintaining stability in time (Sterling & Eyer, 1988). This is sustained by multiple, non-linearly interconnected systems such as the autonomous nervous system (indexed by heart rate [HR] or HRV) that are closely interrelated to psychological processes (McEwen, 1998). However, in case of acute or chronic stress, such as a preterm birth, the overwhelmed organism may display inappropriate responses that could engender deleterious long-term physical effects called "allostatic loads" (McEwen & Stellar, 1993). The allostatic load is known to put individuals at risk for physical and mental illnesses.

HR and HRV (the variability in consecutive beat-to-beat intervals as displayed in an electrocardiogram)

are indicators of the functioning of the autonomous nervous system and thus of physiological stress (Michels et al., 2013). Both indicators allow apprehending the synergy between the brain and cardiovascular control systems by adapting responses to the ever-changing environment (Bates et al., 2011). HR and HRV are thus simple, non-invasive measures to assess stress level and stress reactions. High HRV has been related to higher adaptability of the individuals towards its environment and thus is linked to reduced stress and anxiety (Goessl et al., 2017) as well as to less negative emotions during acute stress (Khodik, 2013). By contrast low HRV has been related to internalizing symptoms (Beauchaine, 2001, 2012, 2015; Beauchaine & Thayer, 2015; Porges, 2007; Vasilev et al., 2009) such as anxiety (Hastings et al., 2008; Kemp et al., 2014; Thayer et al., 1996), depression (Rottenberg, 2007; Rottenberg et al., 2005; Rottenberg et al., 2002), and posttraumatic stress disorder (Cohen et al., 1999).

HRVB – an intervention program on HRV

HRVB programs have been demonstrated to be efficient in increasing HRV and thus in reducing stress and anxiety (Goessl et al., 2017), see below section 3.3 for details. The psychophysiological coherence model (McCraty, 2011; McCraty et al., 2009; McCraty et al., 2006; McCraty & Childre, 2010; McCraty et al., 2012) allows understanding the positive effect of HRVB. It describes a mode of functioning characterized by specific positive patterns of physiological activities (i.e., coherence) expressed in psychological and behavioral systems. More specifically, HRVB influences HRV parameters through the synchronization of the phase relationship between HR oscillations and breathing (at around 0.1 Hz or six breaths per minute) which in turn tends to increase respiratory sinus arrhythmia (RSA) amplitude and, consequently, to heighten the amplitude of HRV (Lehrer & Gevirtz, 2014). Because of increased RSA amplitude, this synchronization also tends to optimize gas exchange at the alveoli and thus to maximize the oxygen supply to the organism (Hayano et al., 1996). These changes may play the role of a virtuous circle, in the sense that the positive changes in HRV due to the synchronization of HR and breathing may act as a positive feedback loop that further increases HRV (Lehrer & Gevirtz, 2014). Moreover, the baroreflex – the reflex that helps regulate blood pressure fluctuations by increasing HR when blood pressure falls and conversely by decreasing it when blood pressure rises – is maximally stimulated by the synchronization (i.e., coherence) of HR and breathing (Lehrer et al., 2003). It has been demonstrated that, probably due to neuroplasticity, training the baroreflex with HRVB sessions leads to increases in baroreflex gain at rest (Lehrer et al., 2003). In this regard, HRVB may produce positive long-term effects on the organism.

2.2 Investigational Product (treatment, device) and Indication

The medical device will be the Nexus product from the Mindmedia company allowing to do biofeedback on HRV. The device measures HRV and respiration rate and provides a feedback to the user regarding how the breathing rhythm changes HRV. HR will be captured by a finger sensor; the Biotrace software will be used to visualize changes in HRV.
The device will be used with authorisation and in conformity with the intended purpose. The Swiss representative, Dr. Eva Otzen, will train the personnel to use the Medical Device (MD). The project's principal investigator, Sébastien Urben, has also received HRVB training by Swiss HRVB specialists : Charly Cungy (Clinique de Belmont) and Jérôme Favrod (Clinique de la Source).

2.3 Clinical Evidence to Date

Qualitative reviews indicate the effectiveness of HRVB in reducing stress and anxiety (Futterman & Shapiro, 1986; Gevirtz, 2013; Tabachnick, 2015). Earlier this year, a meta-analysis (Goessl et al., 2017) identified 24 studies (including 484 participants) using a HRVB program in order to reduce stress and anxiety. HRVB programs varied in intensity ranging from 1 to 50 sessions. Large effect sizes (Hedge's g=.83) were observed both in group comparisons (HRVB *vs* control conditions such as treatment as usual, waiting list, shame-biofeedback, and progressive muscle relaxation) and in time effects (pre-post intervention, Hedge's g=.81). These results indicate that HRVB is a promising intervention program in increasing HRV and thus decreasing stress and anxiety.

Considering using a HRVB program in order to reduce maternal stress due to a preterm delivery, to date, there are no existing studies. However, a pilot study using a HRVB program in women (n=15) suffering from perinatal depression indicated reductions in anxiety and depression symptoms (Beckham et al., 2013), suggesting promising effects in the perinatal period. Further studies are thus warranted in perinatology. Authors of the meta-analysis cited above (Goessl et al., 2017) concluded that HRVB is related to a large reduction of self-reported stress and anxiety and is therefore a promising intervention. However, authors also highlighted the need of better-designed studies including a robust control condition (accounting for the number of contacts with a therapist, for instance) and an assessment of

both short- and long-term effects.

Accordingly, in this feasibility study, we aim to examine the efficacy of a HRVB program on physiological (i.e., HRV) and psychological (i.e., perceived stress and anxiety) stress in mothers who delivered prematurely. We aim at assessing the feasibility of such an intervention program on such individuals in order to compile preliminary data for a bigger scale project.

So far, no clinical trial about HRVB in preterm population (https://clinicaltrials.gov) has been registered.

2.4 Dose Rationale / Medical Device: Rationale for the intended purpose in study (pre-market MD)

Based on a manual (Lehrer et al., 2000), on the recommendations of Prof. Richard Gevirtz (an international expert of HRVB) as well as on advice from Dr. Eva Otzen (the Swiss representative of Mindmedia), the HRVB will be provided daily for 2 weeks.

Before the start of the program and after one week of adherence to the program a session will be conducted with a psychologist (Sébastien Urben) in order to define each participant's individual resonance frequency (i.e., breathing rhythm), using the Nexus program from Mindmedia company. After establishing the individual resonance frequency (i.e., breathing rhythm allowing for cardiac coherence), each participant will be trained with a portable Nexus device which will allow for monitoring adherence and use of the program. We will ask participants to individually perform the HRVB program for 20 min daily over the course of two weeks. To enhance participation, participants will receive a text message. Each participant will be asked to report in a diary all eventual adverse and/or stressful life events.

2.5 Explanation for choice of comparator (or placebo)

Not applicable for this feasibility study.

2.6 Risks / Benefits

First we expect to determine the feasibility of such program in the context of premature delivery. We also expect clinical benefits consisting of an increase of HRV and the associated reduction of stress and anxiety. Participants will not receive a monetary compensation for their participation in this study.
The medical devices (MD) will be used in accordance with its classical use which has received the Central European (CE) certification. This device meets all the requirements of the Medical Device Directive (93/42/EEC, see documentation). Concomitant care will be provided as usual but we do not anticipate possible negative interactions with those treatment. In case of contact with psychiatrist, this information will be notified.

This study has been approved by the "Plateforme de recherche interprofessionnelle" of the Departement Femme-Mère-Enfant (DFME) of CHUV.

Potential disadvantages for the participants are the following: the time taken to participate in the study, the measurement of HRV (wearing the belt, etc.) and potential distress that may arise from completing the questionnaires. For any participant during or after the study who might experience distress related to the participation in the study, Dr Mathilde Morisod Harari (or a delegate) will be available for professional support.

2.7 Justification of choice of study population

The population was chosen because of the potential benefit that such an intervention could engender for mothers who delivered prematurely.

3. STUDY OBJECTIVES

3.1 Overall Objective

Our objective is to assess the feasibility of HRVB and to test its efficacy in the context of premature delivery.

3.2 Primary Objective

The primary objective is to assess the acceptability of the study protocol and the intervention as well as participants' satisfaction with the intervention.

3.3 Secondary Objectives

The secondary objective is to determine the efficacy of HRVB on the physiological (i.e., HRV) and the psychological (i.e., perceived stress and anxiety) aspects of stress in mothers who delivered prematurely.

3.4 Safety Objectives

The study aims to assess the safety and tolerability to use HRVB in such context.

4. STUDY OUTCOMES

4.1 Primary Outcome

Feasibility of the study will be assessed through the number of eligible patients, the rate of study participation acceptance and the rate of drop out. Moreover, satisfaction will be rated on a self-report questionnaire.

4.2 Secondary Outcomes

HRV (i.e., root-mean square differences of successive R-R intervals), perceived stress, and mental health (anxiety, depression, PTSD).

4.3 Safety Outcomes

The safety outcome variables will consist in tolerability of the procedure.

5. STUDY DESIGN

5.1 General study design and justification of design

Ten mothers who delivered prematurely at the maternity ward of CHUV will be invited to undertake a HRVB program. The HRVB program consists of a breathing technique to be performed 20 min daily over the course of two weeks. Physiological (i.e., HRV) and psychological (i.e., self-reported stress and anxiety) stress will be assessed pre- and post-intervention.

5.2 Methods of minimising bias

The equipment providing HRVB, the measures of HRV and the assessment of psychological dimensions are validated and well-established standard measures. The study research team has the required competencies and resources to conduct the study. The PI holds a Good Clinical Practice (GCP) certificate.

6. STUDY POPULATION

6.1 Eligibility criteria

Ten participants from the maternity ward of the University Hospital of Lausanne (CHUV) will be recruited for this feasibility study.

Inclusion criteria are:

- Delivery between 33 and 37 weeks of gestational age;
- Living in Lausanne or surroundings;
- Infant is expected to survive;
- Singleton birth ;
- Consent of mother to participate in the study;
- Sufficient French-speaking to fill out the questionnaires;

- Mother older than 18 years of age.

Exclusion criteria are:

- Infant with cranial abnormality/ neurological squeal such as cystic periventricular leukomalacia and intraventricular haemorrhage;
- Maternal history of drug or alcohol abuse or severe psychiatric disorders before or during pregnancy;
- Infant with congenital anomalies;
- Infant with hearing or vision loss;
- Mother and infant participating in another clinical trial.

6.2 Recruitment and screening

Dr Juliane Schneider will screen medical record for inclusion and exclusion criteria. Then, she will orally inform the mother about the possibility to participate the study and will give the information sheet. The next day a member (Sébastien Urben / Nevena Dimitrova) of the Research Unit of the Child and Adolescent Psychiatry Department will have a phone contact to respond to any questions the mother might have and to obtain oral consent. Then, a meeting will be fixed to obtain written consent and begin the study protocol.

6.3 Criteria for withdrawal / discontinuation of participants

If a participant does not comply with at least 5 training sessions (for 10 min each) she will be excluded from analyses. For this feasibility study, such information is of crucial importance to assess the feasibility of a larger study and the tolerability of the intervention. Thus, the acquired data will be analyzed. If a participant withdraws her informed consent, such participant will be considered as drop out, their data will be analyzed, to assess the rate of drop out.

7. STUDY INTERVENTION

7.1 Identity of Investigational Products (medical device)

This feasibility study represents an open-label trial.

7.1.1 Experimental Intervention (medical device)

The MD providing the HRVB program chosen for this study is the Nexus-4 product from the Mindmedia company. The product will be used according to its standard use.

For the individual training, Emwave products from Hearthmath company will be used according to standard use.

7.1.2 Storage Conditions

Supply, storage, return or destruction of the medical devices are according to standard procedures.

7.2 Administration of experimental and control interventions

7.2.1 Experimental Intervention

Based on a manual (Lehrer et al., 2000), on the recommendations of Prof. Richard Gevirtz (an international expert of HRVB) as well as on advice from Dr. Eva Otzen (the Swiss representative of Mindmedia), the HRVB will be provided daily for 2 weeks.

Before the start of the program and after one week of adherence to the program, two sessions will be conducted with a psychologist (Sébastien Urben) in order to define each participant's individual resonance frequency (i.e., breathing rhythm), using the Nexus program from Mindmedia company. After establishing the individual resonance frequency (i.e., breathing rhythm allowing for cardiac coherence), each participant will be trained with Emwave devices which will allow for monitoring adherence and use of the program. We will ask participants to individually perform the HRVB program for 20 min daily over

the course of two weeks. Five daily sessions of 10 minutes will be considered as the minimum intervention. Each participant will be asked to report in a diary all eventual major stressful life events.

7.2.2 Dose / Device modifications

For this feasibility study, no device modifications are planned. The MD will be used following standard procedure.

7.3 Compliance with study intervention

To enhance participation and compliance with study intervention, participants will receive, daily during the morning, a text message and will be given the opportunity to ask questions. Importantly, the medical device chosen for this study provides information about its use and a feedback to the participant. For the purpose of this feasibility study, data gathered on compliance is key (assessed by the number and duration of training sessions, as well as with complete fulfilling of the questionnaires).

7.4 Data Collection and Follow-up for withdrawn participants

The participants who withdraw their consent or who do not comply with the HRVB program will be considered as dropouts. Intention-to-treat descriptive analyses will be done on baseline information as well as quantifying the training period (if any). All data acquired during the study will be analyzed.

7.5 Trial specific preventive measures

Treatment as usual will be provided to the participants. We did not fix any restriction regarding diet, and/or medication. Medication and stressful event will be monitored and described. The study aims to assess the feasibility of such study in natural settings, thus this event will happen in natural clinical time-course. We did not see any obstacle for our study objectives related to concomitant treatment.

7.6 Concomitant Interventions (treatments)

The treatment usually provided to mothers having a preterm infant will be provided to the participant. No specific intervention on stress and anxiety or HRV is usually provided at the maternity ward of CHUV. All other treatments that participants might follow will be documented.

7.7 Medical Device Accountability

Standard procedure for accurate records and storage will be applied.

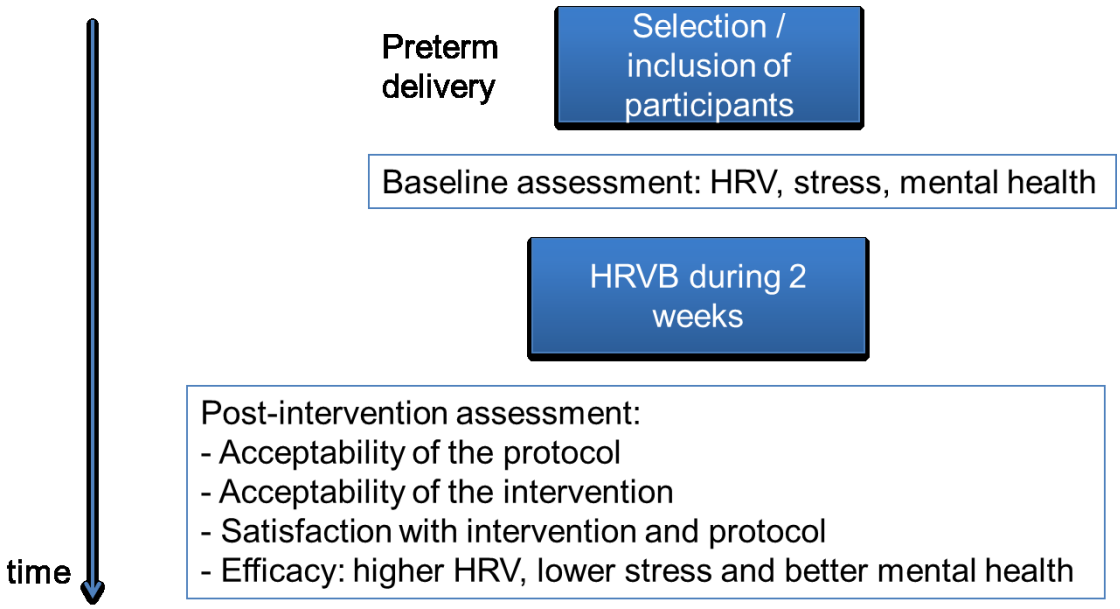
7.8 Return or Destruction of Medical Device

Return or destruction of the medical devices are according to standard procedures and mentioning this in the protocol is enough (no details needed).

8. STUDY ASSESSMENTS

8.1 Study flow chart(s) / table of study procedures and assessments

Study flow chart:



8.2 Assessments of outcomes

8.2.1 Assessment of primary outcome

Feasibility will be assessed trough the number of eligible participants during a month, the ratio of acceptance to participate, compliance with study protocol (number and duration of sessions, fulfilling study questionnaires) and the ratio of drop out. Satisfaction will be measured through a questionnaire (see appendix).

8.2.2 Assessment of secondary outcomes

HRV will be monitored on an electrocardiogram (ECG) for 5 min at rest with the Nexus-4 product from Mindmedia with a standard measurement procedure (sensor at finger). The root-mean square differences of successive R-R intervals (RMSDD) as well as High Frequency (HF) will be used as measures to assess HRV level before and after participation in the HRVB program.

Stress, anxiety and depression symptoms will be measured by self-reports questionnaires (see appendix):

- Perceived stress will be measured on the Perceived Stress Scale (PSS).
- Post-traumatic stress disorder symptoms will be assessed with the Post-traumatic symptoms checklist 5 (PCL-5).
- Anxiety symptoms will be assessed with the State and Trait Anxiety Inventory (STAI).
- Depression symptoms will be assessed with the Beck Depression Inventory (BDI).

8.2.3 Assessment of safety outcomes

Adverse events will be monitored during the training phase. The participant will keep a diary marking any negative events related to the HRVB program. As the program consists of a simple breathing technique, the risk that an adverse event would occur is low. At each session (before the HRVB program and after one week), the trainer will discuss with the participant adverse events that might have occurred. The participant will also have the opportunity to report adverse events by responding to the daily program reminder that she will receive by text message.

Tolerability of the HRVB protocol will be assessed at the end of the study by a qualitative interview.

8.2.4 Assessments in participants who prematurely stop the study

If a participant drops out from the study, an interview will be done to examine the reason of consent withdrawal if the participant agreed to explain her withdrew from the study. The data acquired within the study will be described in the grant proposal.

8.3 Procedures at each visit

8.3.1 Information / consent visit

The participants who fulfill inclusion criteria (without presenting exclusion criteria) will be informed orally about the study by Dr Juliane Schneider and will receive written information. The next day, they will be asked if they have any question about the study and if they agree to participate, written informed consent will be collected.

8.3.2 Pre-intervention assessment

The baseline assessment of HRV will take place at the hospital in a quiet room. Pre-intervention reports on stress, anxiety and depression will be collected with the instruments outlined in section 9.2.2.

8.3.3 HRVB training

In order to familiarize participants with the HRVB program and its apparatus as well as to assess each participant's individual resonance frequency (i.e., breathing rhythm), two training sessions will be provided: one prior to the beginning of the HRVB program (at hospital) and one after one week of HRVB program (either at the hospital or at the participant's home if she has been discharged from the hospital). The second training session aims to optimize adherence to the HRVB program and to reassess participant's resonance frequency.

9.3.5 Post-intervention visit

After two weeks of performing the HRVB program (± 3 days), post-intervention assessment will take place (either at the hospital or at the participant's home if she has been discharged from the hospital). Additionally, a satisfaction questionnaire has to be filled out and a debriefing interview will be conducted in order to discuss the acceptability of the protocol.

9. SAFETY

9.1 Medical Device Category A studies

9.1.1 Definition and Assessment of safety related events

Health hazards which may occur during the participation in the study and that require measures will be documented.
Participants at the beginning of the study will be hospitalized, thus, the likelihood of detecting additional health hazards from the study is low.

9.1.2 Reporting of Safety related events

Severe safety related events refer to (a) incident that necessitate inpatient stay or a prolongation of the inpatient stay which was not planed in the research protocol; (b) lead to severe or chronic handicap or invalidity; (c) caused decease or life threatening; (d) to congenital anomaly or malformation. Such event will be reported to the Sponsor-Investigator within 24 hours upon discovery. The local Ethics Committee will be informed within 15 days. At this time, we did not see any other safety related events that might be documented here.

9.1.3 Safety events detected by chance

Any abnormal ECG patterns detected by chance (no specific assessment by a cardiologist of the ECG measurement) that require medical monitoring and/or intervention will be reported. In such case, an appointment with a cardiologist will be offered to the participant.

10. STATISTICAL METHODS

10.1 Hypothesis

H0: The HRVB program will not show to be feasible and efficient in terms of increasing HRV and reducing stress, anxiety and/or depression.

H1: The HRVB program will show to be feasible and efficient in terms of increasing HRV and reducing stress, anxiety and/or depression.

10.2 Determination of Sample Size

The estimated number of participants is 10 which is considered as sufficient in order to assess the feasibility of the study. Taking into account the meta-analyses on HRVB that reported large effect sizes (Hedges' g >.81) and the fact that we will conduct one-tailed tests, 10 patients is enough to have appropriate statistical power.

10.3 Statistical criteria of termination of trial

No criteria for the termination of the trial are a priori determined for this feasibility study.

10.4 Planned Analyses

Acceptability of the study protocol and intervention as well as satisfaction will be reported descriptively. The inferential analyses will consist in comparing variables (HRV and mental health symptoms) from baseline to post-HRVB intervention using non-parametric Kruskall-Wallis tests. By convention, statistical significance will be set at .05.

10.4.1 Datasets to be analysed, analysis populations

Data from participants who completed the study will be analysed. Drop out data will be used only for descriptive purposes.

10.4.2 Primary Analysis

Nevena Dimitrova will perform the primary analyses.

10.4.3 Safety analysis

The investigator will assess the feedback from the participant about the tolerability of the protocol.

10.5 Handling of missing data and drop-outs

We will analyze data only from participants who completed the study. Missing data from drop out participants will not be replaced but it will be documented.

11. QUALITY ASSURANCE AND CONTROL

11.1 Data handling and record keeping / archiving

Signed informed consent forms along with all physical documentation yielded by participants of this study will be kept in a locked cabinet in a locked room at the Research Unit of the Child and Adolescent Psychiatry Department of CHUV. Participants will be referred by a personal study code, without any personal information that could identify them (i.e., no names, no date of birth). The correspondence between the participant's identity and code will be known only by the principal investigator. CRF data will be first recorded on paper and then entered in an electronic database for analyses (double-check on data entry, by a research collaborator of the research unit, will be conducted to assure correctness).

11.1.1 Specification of source documents

The CRF of the participant will be the source data which will be kept in the research unit of Child and Adolescent Psychiatry Department. Questionnaires assessing stress and mental health will kept in the research unit of Child and Adolescent Psychiatry Department.

11.1.2 Record keeping / archiving

All study data will be archived for a minimum of 15 years (according to local legislation) after study termination or premature termination of the feasibility study. Storage will be handled as described in section 12.1.

11.2 Data management

Data entry into Excel will be double checked (research collaborator from the research unit). Before the inferential statistical analyses, descriptive analyses will be conducted to verify the range of values.

11.2.1 Data Management System

The paper CRF will be entered and then managed on Excel for this feasibility study.

11.2.2 Data security, access and back-up

The data will be saved in a secured database on CHUV's server. The data will be accessible to the research team (members as defined in section 1).

11.2.3 Analysis and archiving

The paper data (consent form) will be stored and archived at the Research Unit of Child and Adolescent Psychiatric Department during the legal period of time (15 years).

11.3 Monitoring

No specific monitoring is planned for this feasibility study.

11.4 Audits and Inspections

The study documentation and the source data/documents are accessible to auditors/inspectors (also CEC and CA) and questions are answered during inspections. All involved parties must keep the participant data strictly confidential.

11.5 Confidentiality, Data Protection

The data will be directly coded (e.g. HRVB_001). The data will be protected and direct access to source documents will be permitted for purposes of audits and inspections (12.4). The data will be accessible only to the members of the research team (as defines in section 1).

11.6 Storage of biological material and related health data

No biological material will be collected. Heath data provided in the CRF will be stored in the Research Unit.

12. FUNDING AND SUPPORT

12.1 Funding

This study will not be externally funded.

13. INSURANCE

As the study refers to risk category "A" no specific insurance will be contracted.

14. REFERENCES

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