Study Protocol and Statistical Analysis Plan

Biologic Mechanisms and Dosing of Active Music Engagement in Children with Acute Lymphoblastic Leukemia and Parents

NCT04400071

US NIH Grant/Contract Award Number: 5R01NR019190-05

Indiana University Protocol NURS-IUSCC-0720
Protocol Version: v.17
October 3, 2024

Principal Investigator:
Sheri L. Robb, PhD, MT-BC
600 Barnhill Drive, NU E433
Indianapolis, IN 46202
317-274-3152
shrobb@iu.edu

1.0 SPECIFIC AIMS

The **purposes** of this two group, randomized, controlled trial are to examine mechanisms of effect and dose-response relationships of AME on child/parent stress over time. Specific aims are to:

- **Aim 1.** Compare the magnitude of change in child and parent cortisol levels between AME and Control during ALL and LyLy treatment.
  - Hypothesis 1.1. Compared to attention control, children in the AME group will have greater pre to post-session percent decreases in cortisol.
  - Hypothesis 1.2. Compared to attention control, parents in the AME group will have greater pre to post-session percent decreases in cortisol.
- **Aim 2.** Examine cortisol as a mediator of AME effects on child and parent outcomes during ALL and LyLy treatment.
  - Hypothesis 2.1: Reductions in child and/or parent cortisol will mediate the effect of AME on child immune function.
  - Hypothesis 2.2: Reductions in child and/or parent cortisol will mediate the effect of AME on child emotional distress and quality of life.
  - Hypothesis 2.3: Reductions in child and/or parent cortisol will mediate the effect of AME on parent emotional/traumatic distress symptoms and quality of life.
- **Aim 3 (Exploratory).** Examine the dose-response relationship of AME on child and parent cortisol during ALL and LyLy treatment.
  - Hypothesis 3.1: While we make no hypotheses for this exploratory aim, we anticipate that AME effects may increase, decay, or remain constant over the course of treatment.

Findings will increase mechanistic understanding of the effects of active music interventions on multiple biomarkers and understanding of dose-response effects. Within the context of the AME intervention, findings from this proposed study on cortisol and immune function will add to our current work on the psychosocial mechanisms of AME (currently funded NR015789), to synergistically create a holistic biobehavioral model of AME mechanisms and effects on interrelated child/parent outcomes. Findings will have direct implications for music therapy clinical practice, and the evidence-based use of music to improve health. Although our specific context is pediatric palliative oncology, findings may be broadly applicable to other music interventions and/or other pediatric populations where interrelated child/parent outcomes are of interest (e.g., other cancers or chronic illnesses).

2.0 ELIGIBILITY CRITERIA

Children and parents (or primary caregiver) will be enrolled as a dyad and must meet the following criteria to be study eligible.

Inclusion criteria:

1. Child is 3 – 8 years of age at time of enrollment
2. Child has diagnosis of standard or high risk, B-cell or T-cell acute lymphoblastic leukemia (ALL) or lymphoma (LyLy)
3. Child is currently receiving induction therapy.
4. One parent (≥18 years of age) can be present for all sessions.

Exclusion criteria:

1. The child has Ph+ ALL.
2. The child has Cushing disease,
3. The child is taking steroid medication for asthma and/or has asthma that is not well controlled.*
4. The parent does not speak English, or
5. The child has a significant cognitive impairment that might hinder participation (determination made in consultation with attending physician, oncologist, and parents).

*Uncontrolled asthma is defined as: 1) Poor symptom control (i.e., frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma),[156] and/or 2) Frequent exacerbations (≥2/year) requiring oral corticosteroids, or

serious exacerbations (≥1/year) requiring hospitalization. For poor symptom control, frequent symptoms are defined as >2 days/week and frequent night waking is defined 1-2x/month for this age group.[157]

3.0 PARTICIPANT RECRUITMENT/ENROLLMENT

Recruitment and Enrollment

The project manager at each site will recruit children/parents during a scheduled clinic visit (before completion of the induction treatment phase, and before the start of consolidation). We will approach children who have a diagnosis of B-cell or T-cell ALL or LyLy. As with our previous/current studies, each site's project manager will work with the hematology/oncology team to identify potential participants. Once identified, the project manager will contact the child/parent to provide initial study introduction/brochure, verify eligibility, and for interested parents, obtain written parent consent for parent and their child and assent for children ≥7 years, following human subjects review committee requirements. Children and parents will be enrolled as a dyad.

Informed consent/child assent procedures will preserve participants' right to refuse participation and guarantees that refusal to participate will not affect their usual medical care. Informed consent for parents will include discussion(s) about the following topics: 1) summary of why the study is being done and why it is considered research, 2) study procedures, including the anticipated length of time that parent/child will participate and what they will be asked to do, 3) potential risks, benefits, costs, and compensation should they choose to participate, 4) confidentiality, 5) their rights as participants, including their ability to stop being a part of the study at any time, and 6) who to contact should questions arise at any point during their time on study.

Child assent (for children ≥7 years old) will include discussion(s) referencing an assent document similar to that of the parent consent form. Children will be presented with this information in a manner that is consistent with their developmental/cognitive abilities. The parent will be present, and the child will be encouraged to ask questions throughout the assent process. Should a child ≥7 years of age decide not to assent, neither the child nor parent will be enrolled in the study (i.e., consent/assent of both parent and child are needed for dyad to be study eligible).

Detailed Recruitment and Retention Plan

The project manager at each site will recruit children/parents during a scheduled clinic visit (before completion of the induction treatment phase, and before consolidation). We will approach children who have a diagnosis of B-cell or T-cell ALL or LyLy. As with our previous/current studies, each site's project manager will work with the hematology/oncology team to identify potential participants. Once identified, the project manager will contact the child/parent to provide initial study introduction/brochure, verify eligibility and explain the study. If the child/parent are interested, the project manager will obtain written parent consent for parent and their child and assent for children ≥ 7 years, following human subjects review committee requirements. Children/parents will be enrolled as a dyad.

In our current R01 and previous studies, the most effective recruitment effort was a health care provider personally introducing the project manager, who then presents the opportunity for involvement in the study. Additional recruitment strategies include: 1) regular in-services for our hematology/oncology staff; 2) laminated study eligibility cards for our hematology/oncology coordinators; 3) study brochures; 4) frequent communication with staff regarding recruitment materials/strategies; 5) use of recruitment logs to track reasons for refusal; and 6) study PI or project manager attendance at weekly rounds.

In addition, we plan to use several strategies to ensure that we recruit and retain adequate numbers of minority participants, including minority staff recruitment, minority recruitment training, racial/ethnically sensitive illustrations on study brochures, and minority recruitment monitoring. We will also work with the Minority Recruitment specialists at the IU Simon Cancer Center to ensure that our recruitment brochures and scripts are appropriately representative of minorities.

During our weekly Executive Team calls (PI, Core Project Manager, and Site Co-Investigators/Project Managers) we will monitor enrollment. Each site co-investigator (or project manager) will complete a weekly enrollment tracking form that includes information on potentially eligible participants, timing for approach, points of contact (study introduction; informed consent), outcomes (follow-up; consented; declined), and reasons for decline. No participant identifiers are included on the form, and tracking forms are stored in a HIPAA compliant data storage website. Weekly review of these reports by the Executive Team ensure that recruitment updates occur regularly and that follow-up with interested

participants is timely. This detailed tracking (including timeliness of activities) also supports our ability to identify and trouble-shoot problems proactively, and maintain steady progress toward our enrollment and accrual goals.

To improve retention, we will use several strategies successfully used in our previous studies, including: 1) personal communication and honoring child and parent preferences when possible; 2) giving parents the option to complete T2 measures by telephone; 3) mailing personalized thank-you notes and reminders of upcoming appointments and data collection times; and 4) letting parents/children keep their music or audio-storybooks kit at the conclusion of the study.

If recruitment rates fall below anticipated rates, we will revisit our recruitment strategies and make modifications based on recruitment log data indicating reasons for refusal. We will also maintain open communication with our hematology/oncology coordinators, physicians, and nursing staff to modify our strategies as needed. If minority recruitment rates fall below anticipated rates we will work with the Minority Recruitment specialists at IU Simon Cancer Center to make recommended adjustments.

4.0 RESEARCH DESIGN, METHODS AND PROCEDURES

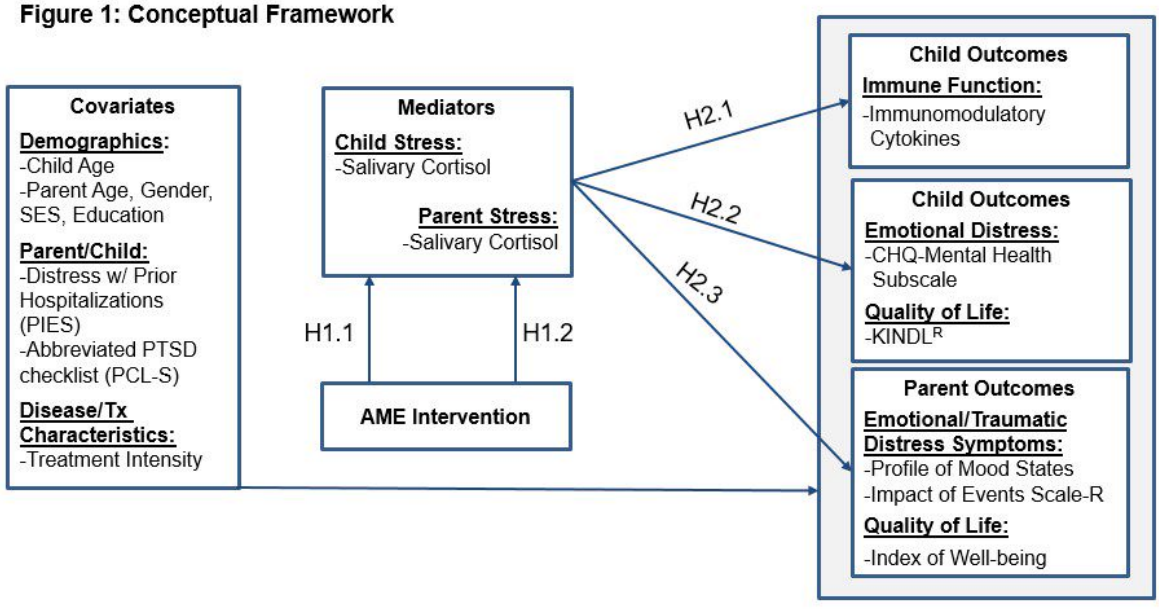
APPROACH

4.1. Conceptual Framework

Our conceptual framework (Figure 1) is based on Robb's Contextual Support Model of Music Therapy[21,47] and further informed by Kazak's Pediatric Medical Traumatic Stress Model,[17] which provides a useful heuristic for understanding short and long-term consequences of pediatric cancer treatment for parents and their child. In our conceptual framework, recurring events related to cancer treatment (i.e., clinic visits, procedures) are viewed as stressful, potentially traumatic events.

Parent appraisal of events as traumatic or not traumatic is influenced by pre-existing factors that serve as covariates in our study. We based covariate selection on published research that indicates higher parent and child distress during cancer treatment is related to: 1) demographics (younger child/parent age, female parent gender, and lower socio-economic status/education),[12,125] 2) higher parent/child distress with prior hospitalizations, and greater traumatic stress symptoms,[16,26,126]and 3) disease and treatment characteristics (treatment intensity).[8-10,107,127-130] In addition, child and parent sex will be important covariates when analyzing our biological data based on evidence that sex hormones play a role in immune response[131,132] and account for differences in salivary cortisol.[133,134] Note that child and parent sex and age are biological variables that we account for in our design and analysis.

Figure 1: Conceptual Framework



We hypothesize that AME directly targets the mediators of child and parent biological stress (cortisol). Our study examines child and parent cortisol as mediators of AME intervention effect on outcomes for child (immune function, emotional distress, and quality of life) and parent (emotional distress, traumatic distress, quality of life). This study will allow us to determine *how* the AME intervention works at the biological level and the intersection of HPA-axis activity

(cortisol) with reductions in emotional distress (emotional/traumatic stress; quality of life) associated with pediatric cancer treatment. Findings will have implications for the use of active music interventions to manage treatment-related distress in other populations.

4.2. Study Design

This is a rigorous two-group, stratified, appropriately powered randomized controlled trial using validated measures (including assays). Children and one parent (enrolled as dyads) will be stratified and randomized in blocks of four to the AME intervention or attention control (audio-storybooks) (see Fig. below). See Treatment Fidelity for discussion on design rigor.

Study Schema

							Session										
Consent	T1	End of Induction^	Stratify & Randomize	→	8 weeks of Consolidation (a)	→	AME	1* ^	2^	3^	4* ^	5	6	7	8*	T2	Parent Interview
						→	Control	1* ^	2^	3^	4* ^	5	6	7	8*	T2	
				→	4 weeks of Consolidation (b)	→	AME	1* ^	2^	3^	4* ^	T2	Parent Interview				
						→	Control	1* ^	2^	3^	4* ^	T2					

Green Shading = Self-Report Measures
Blue Shading = Pre-/Post-Session Salivary Cortisol Collection
* indicates Blood Collection (scheduled lab; all sites)
^ indicates Additional Blood Cortisol Collection (scheduled lab; IU site only)
(a) High Risk B-cell ALL and LyLy and all T-cell ALL and LyLy
(b) Standard Risk B-cell ALL and LyLy

Child/parent dyads will be stratified by child age (preschoolers 3-5 yrs; school-agers 6-8 yrs), site (Riley Hospital for Children, Children's Mercy Hospitals and Clinics, Lurie Children's Hospital, UCSF Benioff Children's Hospital), and treatment intensity (4 weeks; 8 weeks). Both intervention and attention control are standardized and each group will receive one 30-minute session during weekly clinic visits for the duration of the consolidation phase of treatment (4 or 8 weeks; see Study Schema for details). Number of sessions are based on ALL/LyLy treatment duration. Session contact time of 30 minutes led by trained, credentialed music therapists showed benefit in our prior studies.[19-21]

Consolidation duration varies by risk level (4 weeks standard; 8 weeks high), as such, standard risk participants will receive 4 weekly sessions and high risk participants will receive 8 weekly sessions. We are enrolling both standard and high risk ALL participants and participants with LyLy to examine whether dose-response differs based on treatment duration. It is important to examine changes in child-parent stress over the full treatment cycle, and we will control for variations in number of sessions through stratified randomization and our analytic methods.

We chose a randomized, controlled trial over a single-group trial as a control group is optimal for ruling out confounding variables that may impact the relationships between the intervention, mediators, and outcomes. For example, a single-group trial requires a dose be measured to represent the intervention since the variable being mediated must have some variation. Dose may be impacted by several unknown factors that could make interpretation of results difficult.[119] In addition, our prior studies suggest that 1) a usual care condition would likely have high attrition and negatively affect study accrual, and 2) our audio-storybooks attention control condition was acceptable without behavioral benefits.

Baseline data (Time 1) will be collected after consent and before the start of the consolidation phase of treatment. Time 2 data will be collected immediately following the last study session (and no later than 7 days following last study session). Following Time 2 measures, parents randomized to AME will be offered an optional parent interview (completed within 3 weeks of T2 data collection). Parents/children are encouraged to use AME and low dose play activities between clinic visits and self-reported frequency and duration of activities will be collected during each session. Data collection timelines are based on positive findings from our preliminary studies and inform our primary aims that examine mediation. See schema figure and Table 1 for assessment timelines.

4.3. Setting

Young children (ages 3-8 years) and their parents will be recruited from four children's hospitals (two are recruiting sites for our current R01; see support letters). These hospitals are in metropolitan areas that serve large catchment areas. All sites are members of the Children's Oncology Group, and administer chemotherapy according to protocol guidelines, ensuring consistency of treatment across sites. Study conditions and data collection sessions will take place in the outpatient clinic setting. We have successfully conducted sessions/data collection in the outpatient clinic (current R01), and all sites have verified availability of dedicated, private space for these activities.

4.4. Study Participants

Eligibility Criteria. See Section 3.0 for eligibility criteria.

Sample Size. We will recruit a total sample size of 250 child/parent dyads and assume 20% attrition to retain 170 child/parent dyads (85 dyads/group) at Time 2. See PHS Human Subjects Section 4.4 for power analysis.

Feasibility of Obtaining Projected Sample Size. In our Preliminary Study 3 and current R01, which had similar eligibility criteria and study procedures, we had enrollment rates of 80% and 90% respectively.[20] This is consistent with high enrollment rates reported for other pediatric music intervention studies (81-100%).[19,21,135-137] The attrition rate in our current R01 is also low at 10% (90% retained). For this trial, we plan 85% enrollment and 20% attrition due to study location (outpatient clinic) longer study duration (1-2 months), and addition of biologic markers (additional participant burden). Using this estimate, we will need a pool of 250 child/parent dyads across our three sites (four sites as of May 2024) to meet our enrollment goal of 190 child/parent dyads and our retention goal of 170 dyads. To assess our ability to meet these goals, we estimated the pool of eligible participants based on combined admissions data from 2016-2018 at each of the 3 sites. Based on annual admissions data, we estimate that 250 child/parent dyads would be eligible during our 50-month recruitment period (Riley = 50; Children's Mercy = 100; Lurie Children's Hospital = 100). We have well established tracking systems across sites to ensure all study eligible child/parent dyads are informed of the study and recruited if interested. Given that all study sites have consistently high national rankings for patient accrual to clinical oncology trials, our accrual goals are highly feasible.

4.5. Procedures

Our procedures mirror successful strategies used in Preliminary Study 3 and our current R01.

Recruitment & Consent. The project manager at each site will recruit children/parents during a scheduled clinic visit (before completion of the induction treatment phase, and before consolidation). As with our previous/current studies, each site's project manager will work with the hematology/oncology team to identify potential participants. Once identified, the project manager will contact the child/parent to provide initial study introduction/brochure, verify eligibility, and for interested parents, will obtain written parent consent for parent and their child and assent for children $\geq$ 7 years, following human subjects review committee requirements. Children/parents are enrolled as a dyad.

Baseline (Time 1) Measures/Randomization. Following consent, the project manager/co-investigator at each site will arrange a time for parents to complete baseline (T1) measures before their first consolidation phase clinic appointment. A trained evaluator (blind to group assignment) will administer measures in a quiet/private setting and remain available for questions. If in-person measure completion is not possible, we will schedule a date/time for parents to complete T1 measures remotely. Remote measurement completion involves a trained evaluator (from any of our research sites) calling the parent at a time/date identified by the parent, providing instruction on how to access RedCap using a participant-specific link, instructions for measure completion, and then remaining on the phone to answer questions. To ensure protection of private health information (PHI), the Core Project Manager will send participant information (name and phone number) to the assigned evaluator using encrypted e-mail.

After completing measures and before their first consolidation appointment (i.e., once the child's treatment plan and risk level have been confirmed), the project manager will: a) notify the child/parent of their group assignment, b) provide group assignment specific information by text or e-mail (i.e., website link for AME and ASB audio files and/or the Music-Play Program information sheet), and c) schedule Session 1. Only the project manager, PI, statistician, and intervener will know the child/parent dyad's randomization status.

Biologic Sample Collection/Storage during Clinic Visits. A trained evaluator will administer saliva collection questionnaires and obtain salivary cortisol samples from both parent and child. Timing of questionnaires and collections are pre and post-session for the first 4 AME or attention control sessions (both standard and high risk). Parents will also receive a text or e-mail reminder the day before scheduled collections to not eat or drink 60 minutes before their scheduled appointment. Treating physicians, at our three institutions, have assigned clinic days and times (morning vs. afternoon). This will minimize variability in the timing of saliva collection between appointments. We will track day/time of collections and other factors that may contribute to child and parent cortisol interpretation (i.e., sleep, food/drink intake, medications).

We will collect samples using *Salimetrics SalivaBio Oral Swab* for parent, and *SalivaBio Children's Swab* for children. The collection method and sample handling protocol have been validated by Salimetrics for the cortisol analysis. Dr. Russ (Co-I) will develop standard operating procedures for collection and storage of samples and provide training to study evaluators. In addition, Dr. Holochwost (Co-I) will work with Dr. Russ to create child-friendly collection strategies based on his prior work. Each tube will be pre-labeled with a sample ID and date. After each collection, the evaluator will place samples immediately on dry ice in a cooler. Once both pre and post-session samples have been collected, the evaluator will transport samples in the cooler to short term, on-site -80°C storage. About every quarter (3 months), all samples from

our non-IU participating sites will be shipped overnight on dry ice to the Indiana University Simon Cancer Center Translational Research Core (TRC) and stored at -80°C until analysis.

For child participants, 5ml of blood will be reserved from routine draws that are done at the start of each scheduled clinic visit. We use this approach to minimize how often the child's port is accessed to reduce opportunistic infection and stress associated with port access. Blood samples are collected at three time points: session 1 (all participants), session 4 (all participants), and session 8 (high risk participants only). A study member will be present to transport the sample (at time of draw) to the lab for processing. Following study-specific protocols, the blood will be allowed to clot at room temperature and then centrifuged to separate the serum. The serum will be aliquoted, labeled with sample ID and date, and immediately frozen and stored at -80°C. At the end of each month, all samples from our non-IU participating sites will be batch shipped on dry ice via overnight shipping to the TRC and stored at -80°C until analysis. (See PHS Human Subjects and Clinical Trials form for full detailed collection procedures. See Authentication of Key Biological and/or Chemical Resources for methods to ensure identity/validity of cortisol and serum samples).

At our IU site only, we will collect an additional 1mL of blood during routine draws to measure blood cortisol levels at five time points: end of induction clinic appointment, and then sessions 1, 2, 3, and 4 for both standard and high-risk patients. These blood samples will be processed following the BD Vacutainer Rapid Serum Tube guidelines. The serum will be stored as per the above protocol until analysis by the IU Health Pathology Lab. Blood cortisol samples will not be analyzed immediately, but will be stored for future analysis after the child completes consolidation therapy.

Post-Condition (Time 2) Measures. Parents will complete Time 2 measures in the clinic, using a tablet computer, immediately after their last study session (and no later than 7 days of their last study session). Trained study personnel (blind to group assignment) will assist parents to ensure successful access to the Time 2 measures, and then collect the tablet computer after the parent has completed the measures. If in-person measure completion is not possible or if on-site evaluators become unblinded to group assignment, we will schedule a date/time for parents to complete T2 measures remotely. Remote measurement completion involves a trained evaluator (from any of our research sites) calling the parent at a time/date identified by the parent, providing instruction on how to access RedCap using a participant-specific link, providing instructions for measure completion, and then remaining on the phone to answer questions. To ensure protection of PHI, the Core Project Manager will send participant information (name and phone number) to the assigned evaluator using encrypted e-mail.

Parent Qualitative Interviews (AME Only). Interviewing parents about their (and their child's) experience of the AME intervention will allow us to gain a fuller understanding about any perceived benefits, as well as potential mechanisms of action and dosing questions we are examining quantitatively in Aims 2 and 3. For parents randomized to AME, an optional parent interview will be offered and completed within 3 weeks of T2 data collection. The Core Project Manager or assigned interviewer will send the parent a letter with data-generating questions in advance of their scheduled interview so they can provide full rich descriptions of their experience (see Appendix). Members of the research team who have received training in our qualitative interview protocol will conduct interviews in a quiet place in the hospital or by telephone at a time convenient for the parent (see Appendix for interview protocol). We train interviewers across our recruiting sites. For phone interviews, participants may be interviewed by a study team member from another site. All interviews will be audio-recorded and uploaded to a secure, password protected, HIPAA compliant web-based storage system (see Protection against Risk section for more details). All parents randomized to the AME will be invited to participate in the optional interview. Based on prior AME studies, we anticipate that most interviews will last about 30 minutes, and no longer than one hour. Participation is voluntary, and no compensation will be offered to parents for the interview. Interview length is driven by the amount of information the parent wishes to share, and parents can request to end their interview at any time.

Study Condition Procedures. Children/parents randomly assigned to AME or attention control receive the same length of sessions (30 min.) and timing of contact (4 sessions standard risk; 8 sessions high risk). Both conditions are standardized (content, materials, and delivery), and all sessions video or audio-recorded for quality assurance monitoring and data collection purposes (see Intervention Fidelity). Session 3 is video recorded for data collection purposes; all other sessions are audio-recorded. In response to Covid-19, we will be able to offer study condition sessions in-person or virtually (as needed) during clinic appointments. Mode of delivery will be captured in our Redcap database.

Cross-Site Interactions. Our study team is comprised of trained personnel from each of our recruiting sites (Riley Children's Hospital, Lurie Children's Hospital, Children's Mercy Hospital, Benioff Children's Hospital). Participants enrolled at each site may interact with investigators, trained evaluators, and/or trained interviewers from sites other than the enrolling site, constituting cross-site interaction. These cross-site interactions are most likely to occur during Baseline (Time 1) measures, Post-Condition (Time 2) measures, and optional post-condition parent qualitative interviews.

5.0 MEASURES/DATA COLLECTION INSTRUMENTS

Measures. The use of valid, reliable measures help ensure study rigor and reproducibility of results. All measures reflect careful consideration of psychometric properties, sensitivity to change, and response burden. All self-report measures are used in our current R01. See Table 1 for list of measures, psychometrics, and administration schedule. See Appendix for copies of each self-report measure.

Table 1. Measures

Variable(s)	Measure	# Items	Reliability Evidence	Admin. Schedule	Done By
Antecedent Factors					
Demographics	Family Information Form	3	N/A	T1	Parent
Prior Distress w/ Hospitalization Parent Traumatic Stress Screener	Prior Illness Experiences Scale (PIES)[139] Abbreviated PTSD checklist (PCL-S)[140]	13 6	.78† .94†	T1 T1	Parent Parent
Disease and Tx Characteristics	Diagnosis and Treatment Form	2	N/A	T2	PM/Co-I
Mediators					
Child Stress Parent Stress	Salivary Cortisol Edmonton Symptom Assessment Scale (ESAS) Salivary Cortisol Edmonton Symptom Assessment Scale (ESAS)	N/A 5 N/A 3	N/A .68-.80† N/A .68-.80†	Pre/Post Sessions 1-4	Evaluator
Child Stress	Blood Cortisol	N/A	N/A	End of Induction, Sessions 1-4	Nurse/ Phlebotomist
Behavioral Indicators of Stress	Child Engagement Coding[19,21] Parent-Child Interaction Coding[19,21]	N/A N/A	.85* .85*	Sessions 3	Trained Coder
Psychosocial Mediators**					
Family-Normalcy Perspective	Family Management Measure (FaMM) *Family Life Difficulty Subscale*	14	.90†	T1, T2	Evaluator
Parent Self-Efficacy	Parental Beliefs Scale (PBS)	20	.85†	T1, T2	Evaluator
Independent Play	Parent Report Between Session Kit Use	2	N/A	All Sessions	Parent
Child Outcomes					
Child Immune Function	Immunomodulatory Cytokines (Blood)*	N/A	N/A	Pre-Sessions 1, 4, 8	Nurse/ Phlebotomist
Child Emotional Distress	CHQ – *Mental Health Subscale*[141]	16	.81†	T1, T2	Parent
Child Quality of Life	KINDL^{R} [142]	20	.89†	T1, T2	Parent
Parent Outcomes					
Parent Emotional and Traumatic Stress Symptoms	Profile of Mood States-Short Form (POMS)[143] Impact of Events Scale-Revised (IES-R)[144]	37 22	.99** .84-.91†	T1,T2 T1, T2	Parent Parent
Parent Quality of Life	Index of Well-being[145]	9	.93†	T1, T2	Parent

†Cronbach's alpha; *inter-rater reliability; **correlation with POMS
*Blood taken during scheduled draw
**Measures collected in NR015789. Allows for cross-trial comparisons and development of a bio-behavioral model.

Procedures and Materials Collection. Here we describe planned study procedures detailing interactions with study participants, and how members of the study team will obtain specified research material (self-report measures, biological specimens, medical record data, session documentation).

Recruitment and Informed Consent. See Section 4.0.

Biologic Sample Collection (End of Induction; IU Site Only). During the child's last scheduled clinic visit for induction therapy (typically week 4), a study team member will coordinate a 1 ml blood collection that will be drawn during routine labs. See Section 5.0 for more detailed information.

Baseline (Time 1) Measures/Randomization**.** Following consent, the project manager/co-investigator at each site will arrange a time for parents to complete baseline (T1) measures before their first consolidation phase clinic appointment. A trained evaluator will administer measures in a quiet/private setting (at the hospital or by phone) and remain available for questions. If in-person measure completion is not possible, we will schedule a date/time for parents to complete T1 measures remotely. Remote measurement completion involves a trained evaluator (from any of our research sites) calling the parent at a time/date identified by the parent, providing instruction on how to access RedCap using a participant-specific link, providing instructions for measure completion, and then remaining on the phone to answer questions. To ensure protection of PHI, the Core Project Manager will send participant information (name and phone number) to the assigned evaluator using encrypted e-mail.

After completing measures and before their first consolidation appointment (i.e., once the child's treatment plan and risk level have been confirmed), the project manager will: a) notify the child/parent of their group assignment, b) provide group assignment specific information by text or e-mail (i.e., website link for AME and ASB audio files and/or the Music-Play Program information sheet), and c) schedule Session 1. Only the project manager, PI, statistician, and intervener will know the child/parent dyad's randomization status. Based on our prior studies, we estimate it will take the parent 30 minutes to complete the self-report measures.

After randomization, we will assign child/parent dyads a unique study ID number. All participant information and data will be linked with this number to ensure that all information remains de-identified. We will keep a master list of participant names in a separate password-protected file stored in a HIPAA compliant data storage website.

Parents will complete all measures using a tablet computer allowing for direct data entry into our Research Electronic Database Capture (REDCap) site, a HIPAA compliant web-based data management system. In REDCap, all child/parent data are identifiable by study ID number alone. Study team members will have a unique user authorization ID, and password to log into REDCap, and access to data will be restricted based on role-specific user privileges. If paper measures are needed due to internet connectivity, the designated co-investigator will store paper measures and any study-related documentation in a locked cabinet, in a locked office dedicated to our study. Data collected using paper/pencil measures will be directly entered into REDCap by trained personnel and checked for data entry accuracy.

Biologic Sample Collection/Storage during Clinic Visits**.** See Section 5.0.

Video and Audio-Recording Sessions. All study condition sessions (AME, attention control, T1/T2 evaluation) will be audio-recorded for quality monitoring purposes to ensure consistent delivery. In addition, for AME and control session three will be video recorded (rather than audio-recorded) to facilitate collection of child engagement and parent-child interaction data. Following each session, using a password protected computer, the music therapist, attention control intervener, or evaluator will upload a sound (or video) file of their session to a HIPAA compliant data storage site. Once the core site (Indiana University) confirms receipt of the file, the study team member will delete the sound file from their computer desktop, computer trash bin folder, and the audio recorder. Between sessions, audio- and video recorders are stored in a locked cabinet, in a locked office dedicated to the study.

Field Note Entries. Music therapists, attention control interveners, and evaluators will complete field note entries for each study session. Field note entries summarize child/parent responses (including level of engagement and understanding) and any potential external factors (e.g., interruptions, noise) that may have influenced their response. Music therapists and attention control interveners also document parent-reported use of play materials between sessions. Using a secure web-based server, study personnel complete field notes through our REDCap database, which contains no participant identifiers (only study ID numbers).

Post-Condition (Time 2) Measures. Parents will complete Time 2 measures in the clinic, using a table computer, immediately after their last study session (and no later than 7 day after their last study session). Trained study personnel (blind to group assignment) will assist parents to ensure successful access to the Time 2 measures, and then collect the tablet after the parent has completed the measures. If in-person measure completion is not possible or if on-site evaluators become unblinded to group assignment, we will schedule a date/time for parents to complete T2 measures remotely. Remote measurement completion involves a trained evaluator (from any of our research sites) calling the parent at a time/date identified by the parent, providing instruction on how to access RedCap using a participant-specific link, providing instructions for measure completion, and then remaining on the phone to answer questions. To ensure

protection of PHI, the Core Project Manager will send participant information (name and phone number) to the assigned evaluator using encrypted e-mail.

For quality assurance purposes, we will also collect answers to questions provided in Appendix 22 to assess cultural sensitivity of study condition play activities.

Qualitative Parent Interviews (AME only). Parents randomized to AME will be invited to participate in an optional parent interview. Interviews will take place within 3 weeks of Time 2 data collection. Trained qualitative interviewers will conduct parent interviews in a quiet/private setting in the hospital or by telephone at a time convenient for the parent. We train interviewers across our recruiting sites. For phone interviews, participants may be interviewed by a study team member from another site. We estimate interviews will take about 30 minutes to complete (no longer than one hour depending on what parent wishes to share).

Electronic Health Record Data. Following Time 2 data collection, co-investigators at each participating site (Jacob, Stegenga, Shoop) will abstract information about the child's diagnosis and treatment from the electronic health record. Specific information will include their cancer treatment protocol and assigned risk category at the start of the consolidation phase of treatment. These data will then be entered into our REDCap database.

Salivary Cortisol Pre-/Post Collection Questionnaire. To account for factors that may affect cortisol, we will ask consented parents questions about current medications, food/drink intake, smoking, sleep, and activity level before and after each saliva sample is taken (sessions 1-4). We will also ask parents about their child's food/drink intake, sleep, and activity level at the same frequency. Parents will complete these measures using a tablet computer with data directly entered into the REDCap database.

Edmonton Symptom Assessment System (ESAS). This questionnaire will be administered at the same time as pre-/post-collection questionnaires for salivary cortisol and will allow us to examine pre/post session changes in symptoms experienced by the child (e.g., mood, anxiety, pain, fatigue, nausea) and consented parent (e.g., mood, anxiety, and fatigue). Consenting parents will complete items about the child and themselves.

Summary of Collected Materials. Research data for child/parent participants will be obtained using parent-report measures, saliva (child and parent) and blood (child only) specimens, child's electronic health record, and observation. All data documented on paper are kept confidential (labeled only with the child/parent dyad's unique study ID number) and stored in a secure, locked location accessible only to study members. Similarly, all data entered into REDCap are de-identified (linked only to the child/parent's unique study ID number). A master list of participants' names and their identification numbers will be maintained in a password-protected electronic file (stored in a HIPAA compliant data storage site, using a secure web-server) by the PI and Core Project Manager, and available only to members of the research team as needed.

6.0 DETAILED DESCRIPTION OF INTERVENTION

Active Music Engagement (AME) Intervention. AME intervention sessions are designed for delivery by a board-certified music therapist who tailors music experiences to encourage active engagement in and independent use of music play as a strategy to manage emotional distress. During AME sessions, the music therapist provides children/parents repeated opportunities to experience competence, autonomy, and meaningful interactions through music play activities, which leads to active engagement and positive forms of coping. In addition, the therapist provides supportive education about ways music play can be used to manage distress and promote a sense of normalcy both during and between clinic visits.

There are three components to the AME intervention: 1) therapist-led music play activities and sessions, 2) the music play resource kit (to promote independent music play), and 3) tip sheets for parent education and support that focus on information and strategies aimed to help parents use music play to manage their child's distress (the focus of the AME intervention) during clinic visits, and how to use music play at home. A brief summary of each component and general session content follows.

Component I: Music Play Activities. During each session, the music therapist facilitates a 30-minute session using live, interactive music play, guiding the parent/child through AME activities and providing tailored suggestions for independent use during clinic visits. AME activities are theoretically based to promote child competence, autonomy, and supported parent-child relationship in the following ways:

1) Familiar activities (with predictable musical structure) are used to provide structure and increase children's ability to predict what will happen in their environment (predictable environments provide structure that support child competence and encourages initiation of action);

2) Physical activity requirements can be individually tailored to enable even very sick children to successfully engage in activities (leveled activities help ensure success and support child competence);

3) Activities include a variety of materials so children can make choices (opportunities to make independent decisions and support child autonomy); and

4) Activities structure and support reciprocal parent-child interactions (activities and music structure support turn-taking and joint action).

Component II: Music Play Resource Kit. In Preliminary Study 3, we developed a music play resource kit to support independent use of music play between therapist-led sessions. Activities, materials, and music were translated for parent/child use based on therapist-led session activities, and these materials provide enough support for parents/children to self-implement. The kit includes: 1) a professional CD recording of music composed and/or arranged specifically for this project, 2) age-appropriate musical instruments and play materials that correspond with each activity, and 3) activity cards designed to give children/parents at-a-glance information on ways they can use their kit. Activities fall within 5 categories (warm-up, instrument playing, action songs, illustrated songs in storybook form, and wind-down). Within each category, we designed 2 activities (one for older children; one for younger children) to accommodate developmental differences in our targeted sample. All ten activities are offered to all children allowing them to choose activities based on individual preference (developmental stage) rather than biological age. In our preliminary studies, and current R01 study, we found that activities appeal across age groups regardless of intended age. Preliminary Study 3 data also indicated the music play resource kit was highly acceptable to children/parents across our targeted age range, and children/parents initiated kit use between sessions. In this study, children will be given one music play resource kit to take home and a second child-specific kit will remain at the hospital clinic for use during each child's scheduled visits. This is done to (1) encourage AME home use, without parents having to bring the kit to clinic and (2) adhere to hospital guidelines for infection control.

Component III: Tip Sheets for Parent Education and Support. In addition to AME session content, we designed one session planning sheet to help facilitate collaborative assessment of parent/child needs at the start of sessions, and one parent tip sheet. The parent tip sheet was designed to: 1) promote parent competence by teaching parents how they can use music play to support their child during treatment; 2) promote parent autonomy by providing strategies/resources; 3) support parent-child relationships through normalizing, music-based play activities. Tip and planning sheets were piloted in Preliminary Study 3 and are being used in our current R01.

General Session Content: Part 1 Introductions and warm-up activity (5 minutes): At the start of Session 1, the music therapist explains the purpose of AME sessions, presents the music play resource kit, and describes session activities. Following introductions, the child chooses from one of two warm-up activities. The warm-up activity is used to establish rapport among therapist, child, and parent, assess the child's current engagement level, and encourage active involvement. At the start of subsequent sessions 2 to 8, the therapist inquires about independent use of music play, assesses what worked and inquires about preferences and self-identified needs. The therapist also gathers self-report data on the use (frequency/duration) of music play activities since the last session.

Part 2 Child-selected activities (20 minutes): The music therapist facilitates a joint music play session, guiding the parent/child through AME activities and providing tailored suggestions for independent use during treatment. More specifically, the therapist presents the child/parent with a pictorial "music menu" of activity choices and asks the child to choose from one of two activities, in each of three categories. Activity categories include instrument playing, action songs, and illustrated songs in story-book form. Multiple activities (2 per category) are offered to support and accommodate the participation of children who may be experiencing more or less emotional distress, symptom intensity, or changes in functional performance. Because the activities are child-selected, the child can choose and modify his/her level of physical involvement. In addition, the music therapist monitors child behavioral responses and adjusts the tempo (speed) and physical requirements of selected activities to match the child's needs. The music therapist also makes in-the-moment adjustments in the music and activity structure to support and sustain parent-child interactions.

Part 3 Closing activity/tip sheets/resource kit (5 minutes): An interactive "wrap-up" song is used to bring closure to session activities, with the child choosing one of two activities. At the end of sessions one, two, and three the music therapist reviews a different brief tip sheet. Tip sheets content includes information and strategies aimed to help parents use music play to manage their child's distress (the focus of the AME intervention) during clinic visits, and ways to use music play at home.

Attention Control (Audio-storybooks). A trained intervener will deliver the audio-storybooks (ASB) condition, which was designed to control for attention from an intervener, shared parent-child experiences, and audio-visual stimulation. It offers parents/children opportunities to make choices and engage in an age-appropriate, non-music-based play activity. In each session, parents/children choose and listen to one of several illustrated children's books with audio-recorded narration. In our prior work, this condition was acceptable to children and parents and did not demonstrate any significant benefits, making it the best control condition for this study.[24,25]

Treatment Fidelity Strategies. For this study, our team has developed treatment fidelity strategies based on our prior studies (including publication on treatment fidelity)[138] and NIH Behavior Change consortium recommendations. Specific strategies for the five specified fidelity components (design, provider training, treatment delivery, treatment receipt, and treatment enactment) will ensure study rigor and reproducibility.

Design. We are using a rigorous randomized controlled trial design. The AME intervention is a theoretically grounded intervention that has been refined through three previous pilot studies. Similarly, our studies have established the attention control condition as acceptable and effective in controlling for attention from an intervener, shared parent-child experience, and audio-visual stimulation, and shared experiences. Treatment dose is the same within and across conditions, and we have strategies to monitor and confirm (interventionist field note documentation; quality assurance monitoring).

Provider Training. All study personnel will received standardized training specific to their role. We have developed standardized treatment protocols, training manuals, and training content to ensure that all personnel receive the same training over the award period. We will use role playing and ongoing quality assurance monitoring to ensure provider skill acquisition. Music therapists, attention control interveners, and evaluators will be trained separately and participate in separate twice monthly conference calls to avoid cross-contamination and minimize provider drift. Individualized quality assurance monitoring/supervision, along with position descriptions with minimum competencies will accommodate/address provider differences. To avoid implementation setbacks, we will train multiple interventionists and evaluators at each site.

Treatment Delivery. To control for provider differences, reduce differences within treatment, and ensure protocol adherence, we audio-record all sessions and have well established protocols for self and external quality assurance (QA) monitoring. For AME and control sessions one and three, we will use video recorded sessions to monitor delivery (rather than audio-record sessions) because we will video record these sessions for the purpose of collecting behavioral data. Based on study condition and evaluation protocols, we created quality assurance checklists that specify essential content for each AME, attention control, and evaluation session. Self-QA monitoring involves the intervener/evaluator listening to their recorded session and completing the corresponding checklist, noting any discrepancies or challenges encountered with intervention delivery. Simultaneously, trained study personnel complete External-QA monitoring using the corresponding checklist, followed by a review of the intervener/evaluators self-monitoring to note any discrepancies and provide feedback to the intervener/evaluator about observed strengths, any noted protocol deviations, and discussion on how to address any note deviations. We have established thresholds for initial monitoring (first five participants) and ongoing monitoring (every third participant). Separate, twice-monthly calls for each group (involving personnel across all sites) allows for review of study participant progress and role-specific procedures and protocols. The use of different study personnel to deliver AME and attention control and separate conference calls helps to minimize potential for treatment diffusion.

Receipt and Enactment of Treatment. Music therapists, attention control interveners, and evaluators are trained to use active questioning and behavioral observation to assess child and parent comprehension. In addition, each provider completes a session-specific field note entry that summarizes child/parent responses (including level of engagement and understanding) and any potential external factors (e.g., interruptions, noise) that may have influenced their response. To monitor enactment (use of skills learned during sessions), music therapists and attention control interveners document parent-reported use of play materials between sessions.

7.0 POTENTIAL RISKS AND ADEQUACY OF PROTECTION AGAINST RISK

Potential Risks. Risks to child/parent participants are considered minimal and include: 1) breach of confidentiality; 2) increased fatigue for the child or parent as a result of participating in study session activities or completing measures; 3) psychological discomfort for the parent when responding to evaluation questions; 4) child anxiety about placing the Salimetrics SalivaBio swab under the tongue. 5) Blood samples for our study will be collected during a regularly scheduled draw and as such does not introduce additional risk for the child. Protections against these risks are discussed below (see 2b).

Adequacy of Protection against Risks.

Recruitment and Informed Consent. See Section 4.0.

Confidentiality. All child/parent dyads will be assigned a unique study ID number upon enrollment by the coordinating site (Indiana University). To minimize the possibility that a breach in confidentiality will occur, data for this study will be kept separate from any subject identifiers and will be kept on a secure, encrypted data management server. Digital audio or video recordings of child/parent participation in study sessions will also be uploaded to a HIPAA compliant website that is backed up by the university's main computer system. Only the PI, Co-I, Project Manager, and designated research assistants will have access to data. Computers where data will be entered will be accessed through passwords and kept in locked offices. When parents complete paper copies of self-report measures, only their unique study ID number will appear on the measures packet. Once parents complete a set of measures, our evaluators will directly enter their responses into our Research Electronic Database Capture (REDCap) site, a HIPAA compliant web-based data management system. In REDCap, all child/parent data are identifiable by study ID number alone. Study team members will have a unique user authorization ID, and password to log into REDCap, and access to data will be restricted based on role-specific user privileges. At each site, the designated co-investigator will store paper measures and any study-related documentation in a locked cabinet, in a locked office dedicated to our study. During regularly scheduled team meetings, we will refer to participants using their unique study ID number (both in conversation and in resulting minutes). Meeting agendas and minutes, although de-identified, are stored in online on a HIPAA compliant website. Similarly, e-mail correspondence will not include any child/parent identifiers.

Fatigue. Music therapists, attention control interveners, and evaluators will be trained to observe for increasing fatigue and ask parents' to indicate if the child's or their own fatigue is at a level where the activity should be stopped. In addition, sessions will be stopped if the therapist, intervener, or evaluator assesses a level of fatigue in the child or parent that precludes their ability to participate. Children and parents will be informed they can stop the session and/or their involvement in the study at any time.

Psychological Discomfort. Music therapists, attention control interveners, and evaluators will receive specific training in identifying and responding to psychological discomfort related to group assignment or to evaluation. Parents and children will be informed they can stop the session and/or their involvement in the study if they become uncomfortable. Should psychological discomfort be identified, a protocol will be in place to notify the PI. The attending oncologist and nurse on the unit will also be notified of the concern in order to make a decision regarding referral. The PI, core project manager, or site-specific co-investigator will follow up within 24 hours on decisions made. Should any child give any indication the level of psychological distress is at a level of danger to self or others, the child's parent and attending oncologist will be immediately consulted to arrange for an evaluation at Riley Hospital for Children (Indianapolis site), Children's Mercy Hospital (Kansas City site), Lurie Children's Hospital (Chicago site), or Benioff Children's Hospital (Oakland site) unless the parent indicates a preference for treatment elsewhere. In the event that a parent is judged to be a danger to self or others, the child's primary care oncologist will be consulted to arrange an evaluation, unless the parent indicates a preference for treatment elsewhere. Again, parents and children will be informed they can stop the session and/or their involvement in the study at any time.

Physical Discomfort/Risk of Infection. There is minimal risk of physical discomfort and risk of infection to the child during blood draws. These risks will be minimized as the collection is routine, taken from the child's port or line, and done by an experienced technician or nurse.

Anxiety. Evaluators will receive specific training on child-specific strategies for collecting saliva samples to minimize any anxiety about having the Salimetrics SalivaBio swab placed under their tongue. Co-investigator Dr. Holochwost (expertise in child salivary cortisol collection) will work in collaboration with co-investigator Dr. Russ (expertise in sample viability), to develop a child-friendly collection protocol to ensure ease of collection and sample viability. Parents and children will provide samples at the same time, helping to create a shared experience where parents can model use of the SalivaBio swab. As with psychological discomfort, evaluators will also receive specific training in identifying and responding to child anxiety during saliva collections. Parents and children will be informed they can decline saliva collection at any time and/or stop their involvement in the study. Should an evaluator identify significant child anxiety, a protocol will be in place to notify the PI. The attending oncologist and nurse on the unit will also be notified of the concern in order to make a decision regarding referral.

Vulnerable Subjects

This study carries no more than minimal risk to subjects. Rationale for the inclusion of children in this study is that we have developed an intervention that aims to address a significant problem (interrelated child-parent emotional distress)

that affects children (ages 3-8 years) during active cancer treatment and their parents. Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, with peak incidence occurring in children three to five years of age. The active music engagement intervention uses activities that are developmentally appropriate for the specified age group (3-8 years), and would not be appropriate for younger or older children. Children ≥7 years of age must provide assent to participate per requirements for human participants by the sIRB.

Potential Benefits of the Proposed Research to the Subject and Others

The proposed research has potential to address clinically important problems in an understudied age group (children 3-8 years) and in parents of children receiving treatment for ALL or LyLy. For children/parents assigned to the AME intervention, potential problems that may be addressed include child emotional distress, parent emotional/traumatic distress, and parent/child quality of life. For children/parents assigned to the attention control (audio-storybooks) condition, benefits may include distraction and the opportunity to engage in a fun activity of listening to and reading along with illustrated storybooks.

Importance of the Knowledge to be Gained

Findings will increase mechanistic understanding of the effects of active music interventions on multiple biomarkers and understanding of dose-response effects. Within the context of the AME intervention, findings from this proposed study on cortisol and immune function will add to our current work on the psychosocial mechanisms of AME (currently funded NR015789), to synergistically create a holistic biobehavioral model of AME mechanisms and effects on interrelated child/parent outcomes. Findings will have direct implications for music therapy clinical practice, and the evidence-based use of music to improve health. Although our specific context is pediatric palliative oncology, findings may be broadly applicable to other music interventions and/or other pediatric populations where interrelated child/parent outcomes are of interest (e.g., other cancers or chronic illnesses).

8.0 STATISTICAL CONSIDERATIONS and QUALITATIVE ANALYSIS

Power Analysis. The primary goal of this study is to examine mechanisms via the mediation effects of the AME intervention. We will use the percentile bootstrap method to estimate the indirect/mediated effect.[147] The sample size needed for this study is primarily driven by the power needed for the mediation hypothesis in Aim 2. Simulations of the two-path mediation model in Mplus[148] show that 170 subjects are needed to have 88% power to test the total indirect effect using the Sobel approach when the effect of the independent variable (AME in this case) on the mediator is at least medium (13% of variation explained), mediator on the outcome is between small and medium (7% of variation explained), and independent variable on the outcome is small (2% of variation explained). Via simulation, the Type I error with this sample size under a model that assumes no indirect effect is also less than 0.007, which will readily accommodate the multiple comparison adjustments planned below (e.g. with 7 cytokines a conservative Bonferroni adjustment would be 0.05/7 = 0.007). A sample size of 170 will also afford 90% power to detect a medium effect size for H1.1 and H1.2 based on a two-sample t-test with a two-sided alpha level of 0.05. Fitting models that allow for repeated measures across session will result in improved power. Thus, we have chosen a final sample size of 170 (85 child/parent dyads per group) for this randomized trial. Using the percentile bootstrap method instead of Sobel should afford the same or greater power. To allow for approximately 25% attrition, we will recruit a total sample size of 228 child/parent dyads.

Data Management & Analysis. For our current R01 (NR015789), we have already created and successfully implemented secure web-based Research Electronic Database Capture (REDCap) database management systems to capture study data and track and schedule participants' visits. We will review and process data using already-programmed multiple verification and edit-checking programs. We will also conduct rudimentary analyses to ensure that the data were properly collected and to identify any outliers or errors.

Analysis of Biomarkers: Saliva samples cortisol levels will be analyzed using a validated ELISA kit and controls from R&D Systems in the Translational Research Core. The levels of IL-1β, IL-6, TNF-α, IFN-γ, IL-4, IL-10, and IL-13 in patient serum will be analyzed using a Bio-Rad multiplex immunoassay 7-plex kit and controls in the Multiplex Analysis Core. Reproducibility of these kits is validated by the manufacturer and each plate will be run with appropriate standards as well as internal controls to ensure reliability across lots. Kit lot numbers as well as certificates of analysis (provided by the manufacturer) will be kept with the study records. Dr. Kristen Russ, who has over 10 years of experience in laboratory science and toxicology will be analyzing the saliva and overseeing the analysis of the serum cytokines. (See Authentication of Key Biological and/or Chemical Resources for further details). Blood cortisol levels will be analyzed by the IU Health Pathology Laboratory using a Beckman Coulter UniCel Dxl 800 immunoassay system.

Preliminary analyses: Prior to hypothesis testing, we will calculate coefficient alpha as a measure of internal consistency reliability on all multiple-item scales. Construct validity will be assessed by calculating Pearson or Spearman correlations among scales to determine if correlations are in the expected direction. We will present descriptive statistics for the AME group and the attention control group with respect to demographic and baseline outcome variables. We will control for child and parent age, site, risk level (standard or high), greater distress with prior hospitalizations, greater traumatic stress symptoms, time of collection of pre-session cortisol, and child and parent sex in all models. Age, site, and risk level are stratification variables. Time of collection of pre-session cortisol will account for differences based on standard diurnal differences. Although time of collection will be similar within each child, there will likely be between-child differences in time of collection that we will control for in analyses. Child and parent sex and age are important biological variables.

Missing data and multiple comparisons: We will compare all baseline variables between subjects who drop out of the study and those who do not using two-sample *t* tests, chi-square tests, or non-parametric equivalents as appropriate. MPlus software will incorporate participants who drop out before completion by using the MPLUS imputation method to perform a bias adjustment for missing data under maximum likelihood estimation and the assumption that data are missing at random. If we find that missing data are not missing at random, we will use a pattern mixture modeling approach to address; note we expect up to 25% attrition but little to no missing data on instruments (<1%). We will adjust *p* value for multiple comparisons using the Bonferroni method for parent emotional/traumatic distress as there are two outcomes for this domain. For cytokine analyses, there are 7 cytokines of interest, so a Hochberg step-up approach will be used in this setting.

Main analyses: For analyses below, we will analyze as randomized and attempt to collect outcome data on non-completers, following the intent-to-treat principle. For Aims 1 and 2, each outcome will be modeled separately and we will examine sex as a biological variable by include sex as a covariate to control for its relationship with the outcomes and the interaction of sex and intervention group to examine if there are differential effects by intervention group. For Aim 1 (H1.1 and H1.2), the outcome will be the pre to post- percent change in cortisol for each session. A linear mixed model will be fit with the independent fixed effects variables of intervention and session (1 to 4). Subject will be a random effect. We will use an F-test to test the intervention effect. For Aim 2 (H2.1, 2.2, 2.3), our primary goal is to test mediation effects. Mediation effects will be estimated in an ANCOVA setting, fitting the appropriate mediation models using MPlus[146] and then testing indirect effects using the percentile bootstrap approach to estimate the indirect effect.[147] The mediation model with two-path mediation effects specifies that the intervention will act through the mediator on the outcome and also have a direct effect on the outcome. Each outcome model will have 3 key predictors (intervention, two proximal mediators), and control for T1 outcome and covariates described above. For testing cortisol as a mediator, we will use (1) the estimated average percent change estimated from the mixed model, and (2) the % change from pre-session 1 to post session 4. In addition, we will look at child and parent cortisol levels both separately and together (multiple mediation model) in order to fully assess if/how they function together as mediators. Thus for any single outcome, up to 6 models will be examined. For all mediation models in Aim 2, we will assess goodness-of-fit (GOF) using standard GOF measures (comparative fit index, root mean square error of approximation, and root mean square residual). For Aim 3, an exploratory aim, we will use graphical plots and non-linear repeated measures models to model the trend in percent changes in cortisol within and between intervention groups across the 4 sessions for all participants and across 8 sessions for high risk participants.

Qualitative Analysis for Parent Interviews: Prior to analysis, audio-recordings of interviews will be sent for professional transcription by a company that is HIPAA compliant and has vetted procedures for secure, encrypted transmission of audio-files. All transcribed interviews will then be de-identified and checked for accuracy. For analysis, we will use Haase's adapted version of Colaizzi's method of analysis for open-ended interviews to derive the essential structure of parent experiences of the AME.[73,78] This analysis will allow for greater understanding about the potential benefits and mechanisms of action/dosing questions we are studying quantitatively in Aims 2 and 3. Team members trained in phenomenology will conduct the analysis using the following steps: 1) gain understanding of the parent's experience as a whole by reading transcripts in their entirety; 2) identify significant statements and restate them in general terms; 3) formulate meanings; 4) reach consensus on the formulated meanings for each participant; 5) organize the meanings into the main theme categories that consist of related theme clusters; and 6) develop the essential structure of the parent experience. Trustworthiness and credibility of findings will be enhanced by use of an audit trial and involvement of a team during all steps of analysis.

9.0 DATA SAFETY AND MONITORING PLAN

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for **Low Risk Trials.** Investigators will conduct continuous review of data and subject safety. **Quarterly review meetings** for low risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Quarterly** meeting summaries should include review of data, the number of subjects, significant toxicities as described in the protocol, and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

Data and Safety Monitoring Committee
The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

Study Auditing and Monitoring
All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

Data Management/ Oncore Reporting Requirements
The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than 15 days from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

Study Accrual Oversight
Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

Oncore Safety Reporting
In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information.
Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

Monitoring the Safety of Participants. The PI will be responsible for ensuring that the proposed trial is conducted and reported in accordance with the study protocol, Good Clinical Practice (GCP), sIRB, and NIH policy and procedures. Specifically, trial quality assurance as it relates to participant safety will occur in two areas: 1) procedures for the protection of human subjects (consent process, and data confidentiality), and 2) participant safety (adverse events, determination for significant benefit or risk, attention to new literature that indicates an unexpected change to risk profile of study).
Members of the study team fall within the following six groups:

1. Executive Team consists of the study PI (Robb), Core Project Manager (Kendrick), and Site co-investigators (Stegenga, Shoop).
2. AME Music Therapy Team consisting of six board-certified music therapists (2 at each site) who will deliver the intervention, and led by the PI (Robb)

3. Audio-Storybooks Team consisting of six trained interveners (2 at each site) who will deliver the attention control condition
4. Evaluation Team includes evaluators from each site who will be responsible for conducting evaluation sessions and collecting saliva samples, led by Co-I (Stegenga) and Core Project Manager (MacLean)
5. Data Management/Analysis Team consisting of PI (Robb), study data manager, Core Project Manager (Kendrick), and Co-Is (Perkins, Russ, Holochwost).
6. Quality Assurance Monitoring Teams consist of PI (Robb), QA Monitor (MacLean), and trained study personnel who will conduct external quality assurance monitoring of AME, attention control, and evaluation sessions.

Monitoring in these two areas (protection of human subjects and participant safety) will be done by the PI and Executive Team to ensure appropriate confidentiality procedures and consent processes are being followed. The Core Project Manager (Kendrick) will generate annual reports to the Indiana University School of Medicine, Simon Cancer Center Data Safety and Monitoring Committee (IUSM SCC DSMC) for an independent review of study-wide AEs and SAEs and for assessment of risk-to-benefit ratios. IUSM SCC DSMC and the PI will notify the sIRB of any necessary modifications to the protocol based on risk assessment and AEs. No protocol modification will be instituted without sIRB approval. In addition, an independent study-specific safety monitoring committee (SMC) will also be appointed at Indiana University.

Safety Monitoring Committee (SMC). Our SMC will be responsible for reviewing study data once per year and will include PI (Robb), and Co-I/Biostatistician (Perkins), as well as one external biostatistician and one external scientist. Patrick Monahan, PhD, biostatistician and Debra Burns, PhD, MT-BC will serve as external members of the Safety Monitoring Committee for the study. A formal meeting with the SMC members will be held annually to evaluate data quality, subject recruitment, retention, outcomes, adverse events, and protocol deviations.

Protocol Fidelity, Data Integrity, and Data Monitoring.

Protocol Fidelity. For a full discussion of strategies for the five specific treatment fidelity components (design, provider training, treatment delivery, treatment receipt, treatment enactment), please see Section 7.0.

Data Integrity. The data management system for this study will consist of a project-specific database that includes electronic data entry forms and data reporting within Research Electronic Database Capture REDCap, a secure, web-based application for building and managing online databases. The data management system will ensure child/parent participant confidentiality. At the time of study enrollment, each child/parent dyad is assigned a unique study ID number. In addition, each study team member will have a unique user authorization ID, and password to log into the data management system. Access to data will be restricted based on role-specific user privileges.

Parents will complete all measures using a tablet computer allowing for direct data entry into our Research Electronic Database Capture (REDCap) site, a HIPAA compliant web-based data management system. In REDCap, all child/parent data are identifiable by study ID number alone. Study team members will have a unique user authorization ID, and password to log into REDCap, and access to data will be restricted based on role-specific user privileges. If paper measures are needed due to internet connectivity, the designated co-investigator will store paper measures and any study-related documentation in a locked cabinet, in a locked office dedicated to our study. Data collected using paper/pencil measures will be directly entered into REDCap by trained personnel and checked for data entry accuracy.

To minimize the possibility that a breach in confidentiality will occur, data for this study will be kept separate from any subject identifiers and will be kept on a secure, encrypted data management server. Digital recordings of study sessions will be uploaded to a secure, password protected computer server that is backed up by the university's main computer system and after uploading it, the original recording will be permanently deleted. Only the PI, Core Project Manager, Data Management Team, and designated members of the research team will have access to the data. Computers where data will be entered will be accessed through passwords and kept in locked offices.

Data Monitoring. Data monitoring will occur in three stages: 1) field editing for missing data by evaluators; 2) review for completeness/accuracy by the Data Management Team; and 3) Quality Assurance Monitoring Teams will review recorded evaluation sessions to ensure protocol adherence.

Data will be converted to a format (SAS / MPlus) suitable for statistical analysis. Rudimentary analyses by the statistician and/or data manager will be conducted to ensure that the data have been properly merged and to identify any unexpected trends. Periodic reports will be generated to identify outliers, missing data, and other problems of data quality and to document study progress. All data will be reviewed and processed through several verification and edit-checking programs.

Interim Analysis and Stopping Rules. We will not be conducting an interim analysis. The planned study is low risk, and highly unlikely to cause harm that would warrant stopping the study.

Timeline for Reporting Data Breaches or Adverse Events to the NINR.

- Unanticipated problems or unexpected serious adverse events that may be related to the study protocol will be included in annual progress reports, as well as competitive and non-competitive renewal applications, to the NINR. In addition, any changes to our DSM plan, any serious adverse events, or violations of the DSM plan will be reported to the NINR within seven 7 days. Documentation concerning changes to the DSM plan will be countersigned by our Authorized Organization Representative and approved by the NINR before changes are implemented.
- IRB-approved revisions to the study protocol that indicate a change in risk for participants will be reported to the NINR within 7 days. In addition, any changes from the approved involvement of human subjects that would result in an increased risk will require NINR/NIH prior approval.
- A summary of recommendations made by the SMC and (if applicable) the action plan for response will be included in annual progress reports submitted to the NINR.
- Notice of any actions taken by the IRB or regulatory bodies regarding the research and any response to those actions will be reported to the NINR within 7 days.

10.0 REPORTING ADVERSE EVENTS & PROTOCOL DEVIATIONS

An **adverse event** (AE) is defined as any unintended or abnormal reaction or clinical condition that is not of benefit to the participant. Either the response/condition was not present prior to exposure to the study or participation has worsened the intensity or frequency of the response/condition. A **reportable adverse event** is any unintended or abnormal reaction or clinical condition in a subject that (1) places the subject at increased risk of harm **and** (2) was unexpected **and** (3) was related to the research procedures. Extreme fear or anxiety due to study participation may be considered an adverse event in a behavioral/cancer control study. Any breach of patient confidentiality is considered a reportable adverse event.

Expedited Reporting of Adverse Events
Regardless of study sponsorship, the DSMC chair and/or coordinator will review all expedited SAE reports through OnCore, Expedited reports are completed per IRB guidelines and may include the IRB Prompt Reporting form, non-compliance form, AdEERS reports, Med Watch, and additional SAE forms as required by the sponsor. Submission of this information to the DSMC is additional to any other protocol-specified regulatory bodies (e.g., FDA, pharmaceutical company) to be notified. When follow-up information is received hard copies or electronic versions of NCI AdEERS forms, Med Watch and/or other required forms required by the sponsor should also be provided to the DSMC per the current IRB guidelines. The DSMC chair and/or coordinator will review expedited SAE reports weekly, and report findings to the DSMC quarterly.

Reporting of Adverse Events (AEs). Adverse events that occur during AME or Attention Control sessions will be monitored by the music therapist or intervener delivering the sessions. Adverse events that occur during data collection will be monitored by evaluators conducting those sessions/activities. Any concerns will be reported to the PI, site co-investigator, or their designee within 24 hours. Participants will have a local phone number to call if problems occur. If a participant calls and reports an adverse event related to study procedures, it will be brought to the attention of the PI, site co-investigator, or their designee within 24 hours. Minor AEs (e.g. fatigue during completion of study measures) will be reported to the PI and Core Project Manager during weekly Executive meetings and a written AE report will be submitted to the PI and Core Project Manager within 7 days.

All Serious Adverse Events (including serious adverse events related to the study, serious adverse events that are unexpected, and serious adverse events that may affect the study risk/benefit ratio) will be promptly reported within 24 hours to the study PI and reported to the sIRB within 5 working days per IU IRB policy. A written SAE Prompt Reporting Form will be submitted by the site-specific co-investigator to the PI within 3 days with a judgement regarding the relationship of the adverse event to study conditions by the PI or site co-investigator, in consultation with relevant team members. In addition, any major protocol deviation which could impact participant safety, integrity of study data, or subject's willingness to enroll in the study, will require PI or site co-investigators to submit a Prompt Reporting Form to the PI/Core Project Manager within 3 working days, as the PI/Core Project Manager must submit to IU IRB within 5 working days.

All AEs (minor and serious) will be reported to the sIRB annually (continuing review). In addition, the Core Project Manager will ensure all site co-investigators are updated with AE and SAE information at weekly Executive Meetings. The PI will also ensure that adverse consequences due to the study are included in all progress reports and competitive and non-competitive renewal applications to the NIH.

Protocol Deviations
Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

11.0 PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Research Office) and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.