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INSTRUCTIONS:

- Depending on the nature of your research, some sections may not be applicable to your research. These sections can be removed as needed.
- When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.

PROTOCOL TITLE: Music Therapy in Patients Undergoing Pancreatic Surgery (MUSIC PUPS): A Mixed Methods Feasibility Study.

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☒ N/A

VERSION NUMBER:

Include the version number of this protocol if assigned by an outside entity.

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Objectives

The purpose of this study is to determine the feasibility and acceptability of: (1) a tailored music-assisted relaxation and imagery intervention; (2) biological sample collection; and (3) mobile device patient-reported outcome (MDPRO) collection among adults hospitalized for pancreatic surgery experiencing acute pain.

Background

Patients undergoing pancreatic surgery often experience high pain, stress, and anxiety that can contribute to poorer recovery and increased risk of opioid misuse. Interventions that reduce postsurgical anxiety, stress, and pain that are also accessible to a diverse population and individualized to each patient are needed to address this complex problem.

Music therapy has not been investigated specifically in patients undergoing pancreatic surgery. However, several music medicine and music therapy studies in similar populations support the efficacy of music interventions for addressing pain and symptom management in this population. A 2015 systematic review and meta-analysis of 72 music medicine randomized controlled trials (RCTs) initiated before, during, or after surgery found that music interventions reduced postoperative pain (45 RCTs, SMD –0.77 [95% CI –0.99 to –0.56]), anxiety (43 RCTs, –0.68 [–0.95 to –0.41]), and analgesia use (34 RCTs, –0.37 [–0.54 to –0.20]), and increased patient satisfaction (16 RCTs, 1.09 [0.51 to 1.68]) scores. Visual analog scale pain scores were reduced by an average of 23 mm (95% CI 16.9–29.9), and anxiety scores measured by the State Trait Anxiety Inventory were reduced by an average of 6.4 units (95% CI 3.86–8.94). Compared to investigator-selected music, patient-chosen music demonstrated a slightly increased but non-significant reduction in pain as well as a non-significant reduction in analgesia use (Hole et al., 2015). A 2020 systematic review and meta-analysis found that perioperative music interventions significantly reduced postoperative opioid requirements (pooled SMD -0.31 [95% CI -0.45 to -0.16], $p < 0.001$, $I^2 = 44.3$, n = 1398) (Fu et al., 2020).

Within the music therapy literature, investigators have examined the effects of patient-preferred live music (PPLM) and active music engagement among patients undergoing other pancreatic surgeries. Among patients recovering from organ transplant surgery, various small RCTs have demonstrated the efficacy of PPLM delivered by a music therapist for reducing pain, stress, anxiety, nausea, and improving mood and relaxation (Bergh & Silverman, 2018; Crawford et al., 2013; Haack & Silverman, 2017; Hogan & Silverman, 2015; Madson & Silverman, 2010). In a study of 29 adults who received liver and kidney transplants, those who engaged in active music engagement (i.e., singing and/or instrument playing) with a music therapist reported significant reductions in pain and negative affect compared to control (Ghetti, 2011). In a RCT of 44 adult patients on a post-surgical oncology unit, patients who received 20-30 minutes of PPLM (n = 24) reported significant improvements in affect (Global Mood Scale) compared to waitlist control (Merry & Silverman, 2021). Similar studies of PPLM on postsurgical oncology units support its efficacy for improving anxiety, relaxation, and pain (Chaput-McGovern & Silverman, 2012; Yates & Silverman, 2015).

Based on available literature, no prior music therapy studies have investigated the effects of music-assisted relaxation and imagery (MARI) in patients undergoing pancreatic surgery. However, our prior work with this intervention supports its use with this population. In a RCT conducted at our institution, patients receiving palliative care (n = 99) reported clinically and statistically significant mean reductions

in pain intensity (-1.9 points on the 0-10 numeric rating scale) in response to a live 20 min MARI session provided by a music therapist (Gutgsell et al., 2013). In our more recent clinical effectiveness research, among a larger sample of hospitalized adults reporting moderate-to-severe levels (≥ 4/10) of pain, a single session of MARI was clinically effective for reducing mean scores of pain (-2.0 points, n = 416). Patients receiving MARI in this sample reported pain changes of ≤ -2 points in 50% of sessions. More specifically, a single music therapy session was clinically effective for reducing mean pain scores (-1.7 points, n = 70) on a surgical oncology unit with pain changes of ≤ -2 points in 40% of sessions.

Despite several studies supporting the efficacy of music interventions for addressing the needs of surgical patients, biological mechanisms of action remain poorly understood. The most frequently used biomarkers in medical music intervention research have been stress biomarkers including plasma cortisol, salivary cortisol, and salivary α-amylase. While a handful of studies have found significant p-values for the reduction of salivary cortisol and salivary α-amylase in response to music interventions, research using these biomarkers have been limited by non-standardized interventions, small samples, and variation in sample collection (Wong et al., 2021). Recent advances in functional genomic science provide an opportunity to understand gene expression mechanisms. Thus far, these approaches have been applied to mind-body therapies (Bhasin et al., 2013, 2018; Dusek et al., 2008), recreational music making (Bittman et al., 2005, 2013), and music listening (Kanduri, Kuusi, et al., 2015; Kanduri, Raijas, et al., 2015). In a study of 32 healthy volunteers (mean age = 40.8) exposed to a 1-hour stress induction protocol, group keyboard recreational music making (RMM) led to reversal of 19 out of 45 immune response-related gene expression markers in contrast to 6 out of 45 markers in the resting control group and 0 out of 45 in the ongoing stressor group (Bittman et al., 2005). In a similar study of 34 Caucasian adults (mean age = 67.7) with a history of ischemic cardiovascular disease, group keyboard RMM produced changes in expression of 12 pathways governing immune function and genetic information processing compared to 2 pathways in a quiet reading control (Bittman et al., 2013). However, gene expression approaches have not been utilized in the investigation of music therapy or in hospitalized adults.

To support future research of biological mechanisms and scalability in MT, new study protocols must be tested for feasibility and acceptability. Therefore, the purpose of this study is to determine the feasibility and acceptability of: (1) a tailored music-assisted relaxation and imagery intervention; (2) biological sample collection; and (3) mobile device patient-reported outcome (MDPRO) collection in adults hospitalized for pancreatic surgery experiencing acute pain.

Inclusion and Exclusion Criteria

	Inclusion Criteria
1.	Age range: from 50 to 80
2.	Subject is able to speak and understand English
3.	Patient is scheduled to undergo a Whipple procedure or Distal pancreatectomy at UH Cleveland Medical Center with a standardized pain regimen
4.	Patient reports pain intensity of 4/10 or above to research assistant on day 1 post-surgery or any other day post-surgery through discharge

	Exclusion Criteria
1.	Subject has a significant visual impairment that has not been corrected

2.	Subject has a significant hearing impairment that has not been corrected
3.	Subject has a significant cognitive impairment that would prevent subject from participating in the study

Number of Research Participants

We will enroll 30 subjects at UH Cleveland Medical Center (UHCMC).

Recruitment Methods

Patients will be referred by their surgical team prior to their scheduled surgery. A member of the surgical team will tell patients that there is a study they might be eligible for, share the patient flyer with them, and ask if a member of the study team can call them to tell them more about the study. If the patient agrees, the provider will email the study team with the patient's name, medical record number (MRN), date of birth, and upcoming dates for pre-admission testing (PAT) and surgery (if date set). Following the outpatient referral, the research assistant (RA) will review the patient's medical record to pre-screen for eligibility using the eligibility checklist. If the patient meets initial eligibility criteria, the RA will approach the patient over the phone prior to the patient's surgery to explain the study. If the patient is interested in participating, the RA will either (1) meet with the patient at the patient's PAT appointment at UHCMC to obtain full written informed consent or (2) obtain written informed consent over Zoom for Healthcare, depending on the patient's preference.

Setting

Initial consent will take place either in person at the PAT or via a HIPAA-compliant commercial tele-health platform (i.e., Zoom for Healthcare) prior to the patient's surgery. Most subsequent activities will occur at UH Cleveland Medical Center (UHCMC). Confirmation of eligibility (i.e., pain rated ≥4/10 and not admitted to intensive care unit [ICU]) and affirmation of consent to participate, data collection, sample collection, and the in-person MARI intervention will occur within participants' private hospital rooms. We will conduct semi-structured interviews with participants via a HIPAA-compliant commercial tele-health platform (i.e., Zoom Healthcare) or over the phone 1 to 2 weeks after discharge from UHCMC. Following sample collection, blood samples will be temporarily stored within the Connor Whole Health research office in the Wearn building or in the -70 freezer in the Dahms Clinical Research Unit (DCRU) laboratory space in the Wearn building. Later, samples will be shipped to Manoj Bhasin's lab at Emory University for long-term storage and subsequent analysis (Bhasin Systems Biomedicine lab, S335, 1760 Haygood drive, Atlanta, 30322).

Consent Process

Consent will be obtained in writing by the RA and captured in UH REDCap. Initial informed consent will occur before the surgery date either during a PAT appointment in a private clinical or consult room out of the earshot of others to maintain privacy, or via a HIPAA-compliant commercial tele-health platform. Patients will be provided with a copy of the consent form to read prior to the discussion of the study.

The RA will call the patient over the phone prior to their surgery to explain the study. If the patient is interested in participating, the RA will either (1) meet with the patient at the patient's pre-admission testing (PAT) appointment at UHCMC to obtain full written informed consent or (2) obtain written informed consent over Zoom for Healthcare, depending on the patient's preference. The RA will send a copy of the informed consent document to the patient for them to review ahead of the scheduled

informed consent visit. During the consent visit, the patient may ask any questions they have about the study. The RA will answer these questions. The participant's understanding of the study will be documented in the Informed Consent Documentation form in REDCap.

When all questions have been answered, the participant will sign the consent by "making their mark" on the signature line in REDCap to indicate that they understand the document. Patients may participate in the study one time. The study team will send a PDF copy of the signed consent form to the participant via email. A copy of the consent form will be uploaded into the Electronic Health Record.

On day 1 post-surgery, the RA will first check in with the treating physician and/or the clinical nurse prior to approaching the participant to ensure that there is no clinical reason why they think the participant should not participate at that time. Participants admitted in the ICU on day 1 post-surgery, or any other day post-surgery when the study team would initially approach to collect T0 data and provide MARI, will not be approached for further study participation and will be withdrawn from the study.

If the participant is not admitted in the ICU and the treating physician and/or the clinical nurse affirm that it is appropriate to approach the participant, then the RA will check in with the participant in their private room to confirm eligibility, specifically that (1) their pain level is at least a 4 on the 0-10 numeric rating scale, and (2) they affirm that they want to continue participation in the study. The RA will also confirm that the participant is not in too much pain to spend some time answering some questions and to meet with the music therapist.

If the participant's pain is too low or too high to participate, or if the provider or nurse give a clinical reason that the participant should not participate at that time, the RA will return again in 15 minutes to see if anything has changed. At that time, if

- the provider or nurse continue to give a clinical reason that the subject should not participate,
- the participant rates their pain < 4/10,
- the participant indicates that they are in too much pain to participate at that time, or
- the participant is not able to rate their pain due to cognitive or physical limitations,

then the RA will ask the participant if it is ok for the research team to return at another time to see if they meet study criteria and are willing and able to participate in study procedures. If the participant says yes, the RA will return at least 24 hours later and repeat the above steps. If applicable, the RA will return each day that the patient is admitted and study staff are available to repeat the above steps until either (1) the participant's eligibility is confirmed and study procedures begin, (2) the participant says that they are no longer interested in participating in the study at all, (3) the participant becomes ineligible for any other reason (e.g. they are admitted to the ICU, or (4) the participant is discharged. Participants who change their mind about participating (reason 2), become ineligible for another reason (3), or are discharged will be withdrawn from the study. They may still receive music therapy services during their hospitalization after this withdrawal, but these will occur within routine clinical music therapy practice and no data on those sessions will be collected for this study.

The result of both the check in(s) with the provider and with the participant will be documented in REDCap. Participants that continue to meet eligibility criteria on day 1 post-surgery or another day through discharge, and are not withdrawn from the study for the reasons noted above will be considered to have "Initiated study procedures" following enrollment.

Sharing of Results with Research Participants

☒ Results will **not** be shared with research participants

☒ Results will **not** be shared with research participants' doctors

Study Design

We will conduct a single arm non-randomized trial to determine the feasibility and acceptability of: (1) a tailored music-assisted relaxation and imagery intervention; (2) biological sample collection; and (3) mobile device patient-reported outcome (MDPRO) collection among adults hospitalized for pancreatic surgery experiencing acute pain. See Attachment "MUSICPUPS_Schematic" for a graphic representation of the study design.

Study Procedures

Following consent, the RA will ask the participant if they prefer to use their own device or a study iOS device to listen to the MARI recording and respond to the MDPRO surveys. Then, the participant will receive education on how to access the MARI recording and to respond to the surveys based on the choice that they make. The RA will provide a link to education videos on Box.com and a written step-by-step guide, as well as verbal education (see attached videos and step-by-step guides). For participants who choose to use their own device, the RA will create a Box folder for them prior to surgery and have them save a link to this folder on their device home screen before surgery. The RA will also ask participants who choose to use their own device if they would prefer to receive MDPRO invitations via text message or email. This will be recorded in REDCap.

Regardless of which device the participant chooses to use during admission, the RA will encourage them to bring their own headphones to use if that is most comfortable for them (e.g., their own Airpods). However, if they don't have headphones or want to use study headphones instead, study headphones will be provided. If the participant chooses to use their own device and study headphones, the RA will ask the participant if their device has a headphone jack. If it does, they will be provided a set of Apple earbuds during admission. If it does not, they will also be provided a dongle for lightning or USB-C adaptor.

During the consent visit, in addition to the patient education, the RA will ask the participant a series of questions to determine their preferences for music (e.g., genre, artists) and imagery (e.g., a place or time in which the participant feels comfortable). These responses will be recorded in REDCap. After the consent visit, the RA will share the participant's music and imagery preferences with the board-certified music therapist (MT-BC) who is an IRB-approved member of the study team.

Following the participant's surgery, about an hour after eligibility and continued willingness to participate are established as described above, the RA will return to the participants room. This amount of time is necessary to coordinate with the MT-BC, who will not know if the participant is eligible and if they will be providing the MARI intervention until the RA checks in. Before collecting any data, the RA will ask the participant if their pain will permit them to continue and if they would like to proceed. If the participant responds affirmatively, the RA will document this in REDCap and then will proceed to collect baseline (Time 0) patient-reported outcomes (PROs) (i.e., 0-10 ratings of pain, stress, and anxiety) using a REDCap instrument administered on an iPad. The RA will not view the participant's PRO responses. If

the participant is currently utilizing a patient-controlled analgesia (PCA) pump, the RA will collect measures of medication usage from the PCA pump. The RA will also collect a peripheral blood sample using a Spot On Sciences HemaSpot-HF. The research team chose the HemaSpot HF because it is an efficient and less invasive means of collecting capillary blood. Using the HemaSpot HF also poses less risk and discomfort to these patients who recently underwent major surgery. Following baseline measure collection, the RA will leave the participant's room.

Following Time 0, the MT-BC will deliver a standardized 30-minute MARI intervention, personalized to the participant's music and imagery preferences. Prior to the intervention, the MT-BC will verify the participant's music and imagery preferences discussed with the RA during the consent visit. During the MARI intervention, the MT-BC will provide live guitar accompaniment personalized to the participant's music preferences and read from a standardized script directing the participant to relax muscles of the body, practice deep breaths, and explore a relaxing place. This intervention will be recorded live. Following the MARI intervention, the MT-BC will briefly process the participant's experience by asking them how the experience was for them and to describe in their own words how they are feeling after the MARI intervention (please see the attachment "MUSIC PUPS Post MARI Debriefing" for more details). The recorded MARI track will be exported to a Box folder that the participant can access via an app on a study iOS device (e.g., iPod touch, iPhone), or via a web link that is saved as a shortcut on the home screen of the participant's own device. In either case, the participant's MARI use will be tracked in Box.

Immediately following the MARI intervention and post-intervention processing, the MT-BC will leave the participant's room. The RA will then enter the participant's room again. The RA will confirm that the participant is not in too much pain to continue and would like to continue with study procedures, documenting this in REDCap, before collecting post-intervention PROs and peripheral blood smear measures (Time 1). After collecting these measures, the RA will wait in the participant's room for 15 minutes. At 15-minutes post-intervention (Time 2), the RA will again collect PROs and a final peripheral blood smear measure.

After the final PRO and peripheral blood smear collection, the RA will ensure that the participant knows how to access the MARI recording and enter MDPRO measurements using the study iOS device or their own device, and that they have headphones and, if applicable, a dongle, in order to listen to the recording. The RA will instruct the participant to listen to the MARI intervention 3x/day and complete 3 MDPRO measurements each day until discharge. If the participant elects to use a study iOS device, it will be locked to the participant's tray table to prevent it from being lost or stolen during the participant's hospitalization.

Following the collection of blood samples and PROs, the RA will conduct a review of the participant's medical record to collect data on the participant's demographics, clinical characteristics, and pain medications administered pre-intervention. The RA will enter this data into REDCap. Following sample collection, blood samples will be temporarily stored within the Connor Whole Health research office in the Wearn building or in the -70 freezer in the DCRU laboratory space in the Wearn building. Later, samples will be shipped to Manoj Bhasin's lab at Emory University for long-term storage and subsequent analysis (Bhasin Systems Biomedicine lab, S335, 1760 Haygood drive, Atlanta, 30322).

The RA will meet with each participant every day, Monday through Friday, until discharge to troubleshoot any barriers to MARI use or MDPRO collection. Each day, before any troubleshooting or

collecting any data, the RA , like on day one, will (1) check in with the treating physician and/or the clinical nurse; (2) ask the participant if their pain level will permit them to participate; and (3) ask the participant if they still want to participate in study procedures. If the participant responds affirmatively to continuing study procedures, the RA will document this in REDCap and then proceed with troubleshooting and data collection. The RA will record any barriers to MARI use and/or MDPRO collection (i.e., forgot, technical difficulties, off the floor for a procedure) as well as the participant's self-reported use of MARI in the last 24 hours. From Day 2 (i.e., the day after the live MARI intervention) until the participant is discharged from the hospital, participants using a study iOS device will receive three notifications per day (i.e., morning, afternoon, and evening) on the iOS device to complete MDPRO measures, and participants using their own device will receive three email or text invitations (per their preference) to complete the MDPRO measures. The participant's use of the MARI recording will be tracked using file utilization measures available within Box.com. No PHI will be entered into the Box.com folder. The RA will also track the participant's use of pain medications (recorded in the EHR or on the PCA). All data will be stored in REDCap.

On the day of the participant's discharge from the hospital, the RA will collect the study iOS device, if applicable. For those that don't already have the link on their own device, the RA will provide the participant with the MARI recording via email and a Box.com link to allow the participant to access the recording post-discharge. If desired, the RA will also provide the recording via a compact disk. Following discharge, the study coordinator will arrange a time for the participant to complete a semi-structured interview over Zoom. One to two weeks after the participant's discharge from the hospital, researchers will meet with the participant over a HIPAA-compliant commercial tele-health platform to complete a semi-structured interview (see Appendix for interview guide). If the participant is expected to be discharged over the weekend, the RA will provide the MARI recording resources on the Friday before the weekend in which the participant is to be discharged.

Blood sample procedures

All HemaSpot-HF will be prelabeled with a Study ID (e.g., 1,2,3,4, 5), the appropriate study time series (i.e., Time 0, Time 1, or Time 2), and a line for the research assistant to write the date and time the sample was collected.

When collecting the blood sample, the research assistant will follow Spot On Sciences' procedure which can be viewed here (https://www.youtube.com/watch?v=rm8_jfOwlus). These procedures are as follows:

1) Put on a pair of protective gloves;
2) Clean and sanitize a tray table on which to place the HemaSpot materials;
3) Lay out the materials from the HemaSpot kit on a tray table in the participant's room;
4) Clean the participant's finger using an alcohol wipe;
5) Remove the cap from the lancet and position the end against the inside tip of the middle or ring finger;
6) Press the lancet firmly on the participant's finger until it activates with a click;
7) Wipe away the first drop of blood with a sterile gauze;
8) Position the lanced finger over the center of the HemaSpot;
9) Provide gentle pressure on the end of the finger, and let three drops of blood drip from the finger onto the center of the HemaSpot;
10) Wait one minute for the wicking process to complete;
11) Bandage the participant's finger;

12) Close the HemaSpot firmly ensuring that the latch is secure.

These steps will occur at Time 0, Time 1, and Time 2, with the RA sampling a different finger from the participant at each time. The RA will note any challenges to blood sample collection (e.g., participant discomfort, device malfunction, participant refusal) and record these in REDCap following the procedure.

Following blood sample collection, the RA will ensure that the samples are properly labeled and their collection are noted in REDCap. The three samples will be placed in a secure padded envelope and locked in the Connor Whole Health Research Office in Wearn 548 or in the DCRU lab in the Wearn building until they are shipped to the Emory lab for analysis via UPS.

Suicidal Ideation, Acute Anxiety and Adverse Event Mitigation Plan

If a patient reports suicidal ideation while admitted at any point during the study, study staff will immediately contact the clinical care team and make a note in the patient's EHR. If the patient reports an anxiety score greater than or equal to 7/10 on the numeric rating scale during the study, study staff will make a note in the patient's EHR documenting the patient's anxiety score. The clinical care team will follow their intervention protocol to address the patient's situation.

Interview procedures

Interviews will take place over a HIPAA-compliant commercial tele-health platform (i.e., Zoom for Healthcare) or over the phone one-to-two weeks after the participant is discharged from the hospital. During that interview, a researcher will ask the participant about their experience in the study and what they thought about the MARI intervention. The researcher conducting the interviews remotely will be in a private room when interviewing the participants and will be certified in human subject protection and GCP, researched credentialed if applicable, and on the study personnel table. The interview will take about 30 minutes and will be recorded and then transcribed by hand.

Study Timeline

	Pre-Screening	Consent & Education	Time 0	MARI	Time 1	Time 2	Day 2 to discharge	Interview
Estimated time requirement of visit	15 min	25-40 min	5 min	30 min	5 min	5 min	15 min 3x/day	30 min
Data Collection			X		X	X	X	X
Consent process		X						
Mobile device education		X						
Music therapy intervention				X			X	

Data to be Collected for your study (AFTER consent and HIPAA Authorization have been obtained)

Demographics

1. Age
2. Sex
3. Race
4. Ethnicity
5. Marital status

Clinical characteristics

1. Principal diagnosis
2. Secondary mental health diagnoses (if applicable)
3. Other services provided during hospitalization (e.g., art therapy, psychiatry, spiritual care, palliative care, social work)
4. Admission date
5. Pain medications administered (name, route, quantity, dose, time)
6. Surgery date
7. Surgery type
8. Significant surgical complications
9. Hospital floor
10. MARI intervention date
11. Music preferences
12. Imagery preferences
13. Discharge date

Patient reported outcomes pre-intervention (Time 0), post-intervention (Time 1) and 15-minutes post-intervention (Time 2), and three times per day (i.e., morning, afternoon, and evening) until the participant is discharged.

1. Pain (0-10)
2. Stress (0-10)
3. Anxiety (0-10)

Feasibility measures

1. Reasons for not completing MARI intervention (if applicable)
2. Reasons for not completing peripheral blood smear (if applicable)
3. Dates/times of accessing the MARI recording during participant's hospitalization
4. Self-reported use of MARI recording during participant's hospitalization
5. Reasons for not using MARI recording (if applicable)
6. Reasons for not entering MDPRO data (if applicable)
7. Reasons for study withdrawal (if applicable)

Semi-structured interview

1. Audio recording
2. Transcript

Biological samples pre-intervention (Time 0), post-intervention (Time 1), 15-minutes post-intervention (Time 2).

1. Peripheral blood sample

Data Analysis Plan

In anticipation of a dropout rate of 33% following admission to the hospital (i.e., participants either not ever meeting pain criteria or choosing not to participate), we decided on a sample size of 30 participants with a plan to complete study procedures among the first 20 participants meeting full eligibility criteria. We based our sample size of 20 and definition of feasibility on prior research examining the feasibility of biological sample collection with music therapy (Holochwost et al, 2020). We have no prior experience using the HemaSpot HF for sample collection nor with delivery of the MARI intervention to this population and plan to start with a small sample size in order to refine procedures for a larger study. We hypothesize a 75% feasibility threshold for complete live MARI intervention delivery, PRO collection, and biological sample collection. We would consider failure to be completing less than 15/20 MARI interventions, 15/20 complete sets of PROs at Time 0, Time 1, and Time 2, 80% of MDPRO measures over the duration of the participant's hospitalization, and 45/60 blood sample collections.

We will use descriptive statistics (e.g., counts, percentages, mean, standard deviation, and median) to summarize participants' demographics and clinical characteristics (obtained from EHR), as well as feasibility measures including rates of enrollment, attrition, intervention participation, MARI recording use, biological sample collection/viability, and PRO collection. We will determine the feasibility of biological sample viability by quantifying whether individual participants provided enough biological samples for eventual testing. No formal hypothesis tests (e.g., linear mixed effects models) will be conducted on changes in PRO data as this is a feasibility study.

Blood sample analysis plan

We are not collecting genetic data. We are not performing any genetic profiling. We are performing gene expression analysis, and this is different from genetic profiling. This is a pilot study to collect information in preparation for an appropriately powered study. To establish procedural elements, it is necessary to test procedures including the MARI intervention, peripheral blood sampling, and mobile device patient-reported outcome collection as these have not been utilized in prior studies with this population. We have already consulted with statisticians and based on our previous findings in music intervention, we need 87 pre- and post-measures on subjects for the fully powered study. After this pilot study, we intend to launch a multi-center feasibility study in collaboration with other institutions.

We will plan on conducting the following gene expression analyses as specified for all three-time points (Time 0, Time 1, and Time 2). The gene expression analysis will be performed at Bhasin Systems biomedicine lab at Emory University.

A large part of the human genome is transcribed into various forms of RNA, and the global gene expression profile (GEP) changes measure expression changes in genes over time due to an intervention.

Accordingly, our long-term goal of this line of research will be to examine whether pain intensity changes after the MARI intervention are associated with specific changes in gene expression profiles (GEP) and pathophysiologic pathways that correspond with the elicitation of the relaxation response (Bhasin et al., 2013, 2018; Dusek et al., 2008).

Our prior work was conducted among healthy adults (Bhasin et al., 2013; Dusek et al., 2008) or hypertensive patients (Bhasin et al., 2018) living in the community using PaxGene tubes to collect whole blood. In the intervening years, the technology of dried blood spot (DBS) collection of samples has improved and has been used for GEP analysis.

Thus, for the current feasibility study with 30 pancreatic surgical patients with acute post-operative pain, we are primarily interested in understanding the feasibility of collecting the HemaSpot samples from this population and whether the samples collected will be of sufficient quality to allow for gene expression profile testing. The HemaSpot sample will be sent to Dr. Bhasin's lab at Emory University for RNA sequencing based transcriptome profiling. The transcriptome profiling will be performed using paired-end RNA sequencing that allows for the measurement of the expression profile of ~30,000 human genes with high sensitivity and specificity. Briefly, sequencing libraries of Poly A selected mRNA will be generated from the double-stranded cDNA using the Illumina TruSeq kit according to the manufacturer's protocol. High-quality libraries will be sequenced on an Illumina Novaseq 6000 to achieve comprehensive coverage of measuring the expression of all genes. **The assay can only measure the expression of genes but cannot reveal the identity/race/gender of the subjects.**

The Raw sequencing data will be processed to remove any adaptor, PCR primers, and low-quality transcripts. After alignment, the gene expression levels will be normalized and compared among the baseline and post-intervention samples to identify genes that are significantly modulated by the intervention. The comparison will be performed by implementing linear data modeling algorithms comparing the mean and variance among the groups. We will perform a focused analysis on immune and inflammatory response-related genes as our previous analyses depicted that mind-body interventions deliver beneficial effects by affecting these pathways. Additionally, to understand the detailed mechanism of intervention, we will perform pathways enrichment and interactive network analysis.

Although the size of the feasibility proposal is small, we contend that it is worth conducting the GEP for each of the 30 participants across the 3-time points. However, with the small sample it will be beyond the scope of our study to confidently compare the GEP from T0 to T1 to T2. That type of analysis would be conducted in a future randomized trial with a comparison group.

Once the dried spots arrive at Emory University, two will be processed for RNA extraction, followed by library preparation and whole genome RNA sequencing to measure a profile of 30,000 genes. Lab technicians will extract RNA from the dried blood spots (DBS) and prepare RNA sequencing (RNAseq) libraries. This process will occur in three steps: (1) RNA extraction and isolation, (2) RNAseq library preparation, and (3) Sequencing.

1. RNA extraction and isolation. The RNA will be quantified using Qubit (Thermo Fisher Scientific) and quality assessed by RNA bioanalyzer chips (Agilent). See attachment "NEB Protocol" for more details on RNA extraction and isolation.
2. RNAseq library preparation. The lab technicians will use the New England biolabs kits. First, they will remove ribosomal RNAs using ribosomal depletion kit (NEB#E6310) and then prepare the RNAseq library using the NEBNext® Ultra™ II Directional RNA Library Prep with Sample Purification Beads (NEB#E7765). The technicians will quantify the library using qubit and checking the quality HS DNA bioanalyzer chips (Agilent). See attachment "RNA Extraction and Isolation from HemaSpot" for more details on the RNAseq library preparation protocol.

3. Sequencing. Once the RNAseq libraries are made, the lab technicians will sequence them using NextSeq 500/550 mid output kits – 150 cycles (Illumina).

Qualitative analysis plan

Interviews will take place via a HIPAA-compliant commercial tele-health platform (i.e., Zoom for Healthcare) and be recorded then transcribed by hand. The RA, who will not conduct any interviews, will proof transcripts against the original recordings for accuracy. The transcribed interviews will be imported into the qualitative software program NVivo for analysis. At least two individuals experienced in qualitative data analysis will perform a line-by-line review and coding of each transcript independently using a constant comparative method of qualitative data analysis (Hseih & Shannon, 2005). The initial coding will consist of reading the narrative text and highlighting words or phrases that capture the experience with music therapy. Text will be coded as themes as identified from the narratives and will be organized into meaningful categories and subcategories. In the final step, a table with categories and subcategories of data, along with definitions for each category, will be constructed consistent with study objectives. All data from the interviews that appear to be directly related to the study aims will be extracted.

Strategies to optimize validity will include reviewing the coding among all coders, refining the coding until there is agreement. Members of the research team will review findings for accuracy of generated themes, interpretations of the data, and conclusions.

Risks to Research Participants

The participant may not like the MARI intervention included in the study. In that event, participants may ask the MT-BC to stop the intervention and choose not to participate in the rest of the intervention. The probability of this event is low, however, as it has not occurred in any prior music therapy studies and its occurrence is rare in music therapy practice. It is possible that the participant may experience discomfort providing peripheral blood samples via finger prick. A breach in participants' privacy and confidentiality may occur as a result of participating in this research study.

Provisions to Protect the Privacy Interests of Research Participants

All attempts will be made to ensure participants' privacy. The referrals will come from the participant's medical team. The participant's name will only appear on the consent form and the linking log. The linking log that identifies the participant's study ID to identifiable data will be stored on a password-protected, encrypted computer or secure server. All data that is stored in REDCap will identify the participant by the number assigned to them at the beginning of the study. Informed consent will occur in a private clinical room or consult room out of the earshot of others to maintain privacy.

Only aggregate data will be presented or published and will be presented such that individuals cannot be identified. Only IRB-approved study personnel will have access to participant data. All study personnel will be required to be certified in the protection of human subjects throughout the study.

Identifiable information will not be reused or disclosed to any person or entity outside of University Hospitals other than those identified in the protocol, except as required by law, for authorized oversight of the research study, or as specifically approved for use in another study by the IRB.

Potential Benefit to Research Participants

Although not guaranteed, there is the possibility that the MARI intervention may reduce pain, anxiety and stress after their surgery. Furthermore, future surgical patients may benefit from the knowledge gained from this study.

Withdrawal of Research Participants

The study doctor or the sponsor can withdraw participation of research participants at any time without their consent for the following reasons:

- If the patient is admitted to the ICU following surgery and remain admitted to the ICU on the day when study procedures would typically begin.
- If, after the first day participation, the participant's clinical condition deteriorates enough that they are transferred to the ICU.
- If it appears to be medically harmful to the subject;
- If the subject fails to follow directions for participating in the study;
- If it is discovered that the subject does not meet the study requirements;
- If the study is canceled; or
- For administrative reasons, including competitive enrollment - the target number of subjects has entered the study.

Alternatives to Participation

Instead of participating in this research study, patients can continue to work with their care team to manage their pain.

Costs to Research Participants

There is no cost to participate in this study.

Research Participant Compensation

Participants who complete the semi-structured interview will receive a $25 gift card.

Provisions to Monitor the Data to Ensure the Safety of Research Participants

The study PI will monitor the study to ensure data integrity and the safety of the participants. The study coordinator will review the data for discrepancies on a regular basis and will review the study records for compliance with IRB requirements. The study team will hold regular weekly meetings to review study progress and any issues that may come up regarding data integrity and completeness.

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