

BMJ Open Study protocol for a multicentre randomised controlled trial studying the effect of a music intervention on anxiety in adult critically ill patients (The RELACS trial)

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ABSTRACT

Introduction Anxiety is common in critically ill patients and has likely become more prevalent in the recent decade due to the imperative of the recent Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients (PADIS) to use low levels of sedation and strive for wakefulness. However, management of anxiety has not been included in the PADIS guidelines, and there is lack of evidence to treat it in spite of its growing importance. Administration of sedative and analgesic medication is often chosen to reduce anxiety, especially when associated with agitation. Sedatives are associated with prolonged mechanical ventilation, delirium and muscle wasting and are therefore preferably minimised. Previous studies have suggested positive effects of music interventions on anxiety in the critically ill. Therefore, we aim to study the effect of music intervention on anxiety in adult critically ill patients.

Methods and design A multicentre randomised controlled trial was designed to study the effect of a music intervention on the level of anxiety experienced by adult patients admitted to the intensive care unit (ICU). One hundred and four patients will be included in three centres in the Netherlands. Patient recruitment started on 24-08-2020 and is ongoing in three hospitals. The primary outcome is self-reported anxiety measured on the visual analogue scale. Secondary outcomes include anxiety measured using the six-item State-Trait Anxiety Inventory, sleep quality, agitation and sedation level, medication requirement, pain, delirium, complications, time spend on mechanical ventilation, physical parameters and ICU memory and experience.

Ethics and dissemination The Medical Ethics Review Board of Erasmus MC University Medical Centre Rotterdam, The Netherlands, has approved this protocol. The study is being conducted in accordance with the Declaration of Helsinki. Results of this trial will be published in peer-reviewed scientific journals and conference presentations.

Trial registration number NCT04796389.

INTRODUCTION

Anxiety is common in critically ill patients.^{1 2} The incidence of anxiety in the critical care

Strength and limitations of this study

- This is a multicentre randomised controlled trial that studies the effect of a music intervention on the anxiety in critically ill patients in the Netherlands.
- The music intervention has no side effects with strong potential for benefit for an as yet difficult to manage issue (anxiety) at the intensive care unit.
- Patients and professionals cannot be blinded for the intervention which may lead to performance and detection bias.

population ranges from 30% to 80%.^{1 3} This wide range may be caused by the fact that routine assessment of anxiety is currently not part of the standard care and is based on clinical assessment.⁴ Anxiety in the intensive care unit (ICU) may be important beyond the argument of patient comfort, since anxiety can negatively influence the body's homeostasis and behavioural, physiological and cellular activity.^{5 6} Furthermore, anxiety and pain are strongly correlated in the ICU population and may reinforce each other leading to higher sedative and analgesic requirement.⁷

Administration of sedative and analgesic medication is often chosen in order to reduce anxiety and thus improve patient comfort.² However, these medications are known to have negative side-effects, such as prolonged mechanical ventilation and ICU length of stay (LOS).⁸⁻¹³ Furthermore, benzodiazepines are associated with development of delirium, which can negatively affect prognosis.^{14 15} Currently, alternatives are scarce and no guideline recommendations exist for non-pharmacological treatment of anxiety in the ICU.⁴ Moreover, the Clinical Practice Guidelines for the Prevention and Management

of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients (PADIS) guidelines strongly recommend to avoid sedatives, especially benzodiazepines, whenever possible due to the above-mentioned negative effects. The more recent tendency to strive for wakefulness in ICU patients may add to the incidence and severity of anxiety. The recommendation to avoid benzodiazepines is at odds in clinical practice with the wish of healthcare providers to alleviate anxiety, stress and other discomforts and therefore represents a clinical dilemma. In spite of acknowledgement in the PADIS guidelines of anxiety as a relevant clinical issue, evidence on management is scarce and not evaluated in these guidelines. Only one, adequately powered previous randomised controlled trial by Chlan *et al*¹⁶ exists that assessed patient directed music intervention on anxiety. Although this trial reported a positive effect of the intervention, it is likely that efficacy of the intervention is highly context specific and therefore may not be reproducible in other patient populations (eg, different indications for ICU admission, sedation/pain protocols used, frequency of music applied, type of music applied, role of music in the society and so on). Further, higher level of evidence is obtained by more than one trial showing efficacy. In summary therefore, management of anxiety is understudied and probably underdetected, with a dire need for effective interventions that are context independent regarding efficacy.^{3 7}

Rationale

Music as a non-pharmacological therapy has been widely studied in the medical field and has shown its effect in various settings. In the surgical population, large studies have shown significant effects of music in reducing perioperative anxiety and pain, intraoperative sedative requirement, postoperative opioid requirement and postoperative neurohormonal stress response.^{17–19} Several studies and systematic reviews suggest positive effects of music interventions in the critically ill, on pain, anxiety, stress, vital signs, sedative and analgesic medication requirement.^{6 16 20–24} Additional advantages of music are that it has no known negative side effects and can easily become cost-effective, when shown effective. However, evidence on music to decrease anxiety in wakeful ICU patients is scarce and therefore not recommended by guidelines.²³ Considering this, we hypothesise that music intervention can have a positive effect on anxiety in critically ill patients and aim to study the effect of music intervention in these patients.

Primary objective

The primary aim of this study is to investigate the effect of a music intervention on anxiety in adult patients admitted to the ICU.

Secondary objective

To investigate the effect of music intervention on sleep quality, agitation and sedation level, sedative and opioid

medication requirement, pain, delirium, complications related to agitation, time spend on mechanical ventilation, physical parameters and ICU memory and experience.

METHODS AND ANALYSIS

Study design

The RELACS (REsuLt of music intervention on Anxiety in Critically ill PatientS) trial is a multicentre randomised controlled trial using a two parallel arm design initiated by the Erasmus MC, Rotterdam.

Eligibility criteria

Critically ill patients aged 18 years or older are eligible for inclusion in the study when meeting the following criteria; haemodynamically stable, communicable (Richmond Agitation and Sedation Scale (RASS) of at least –2, 24 hours before intended inclusion: meaning the patient is at least briefly awakened with eye contact to voice) and is considered to be able to provide information regarding his/her anxiety level, an expected ICU stay on randomisation of at least 48 hours, and a written informed consent is acquired from the patient or legal representative. Exclusion criteria are: severe hearing impairment (defined as no verbal communication possible), neurological condition (eg, severe stroke), when deemed to interfere with processing of music (eg, not applicable to patients with minor stroke in past medical history without significant residual neurological deficits; those patients could be included), insufficient knowledge of the Dutch or English language for informed consent and participation in another study that may possibly intervene with the primary outcome.

Randomisation, blinding and treatment allocation

Parallel randomisation is used to allocate subjects with an equal allocation ratio in either the intervention or the control group. The random allocation sequence using random block size randomisation and stratification by centre is generated by an online web-based randomisation programme (ALEA; FormVision, Abcoude, The Netherlands). Allocation concealment is ensured since the randomisation code is released after the patient is included in the trial. As the intervention is without risks and cannot be blinded, it will be in no case necessary to break the randomisation code. As for most music intervention studies, patients and personnel cannot be blinded for the intervention. The primary outcome is a previously validated patient-reported anxiety scale (VAS-Anxiety) and the secondary outcomes are also partly patient reported (State-Trait Anxiety Inventory (STAI-6), sleep quality and patient experience) and therefore not possible to blind for these outcome assessment. In order to prevent bias due to non-blinding of the outcome assessor (member of the research team), the patient reported outcomes come with a clear description of how they should be assessed (each form for each variable will start with how the variable should be assessed).

Treatment arms

This randomised controlled study consists of two groups; the music group and the control group. The music group will receive music through over-the-ear headphones, which do not contain any absorbable materials and can be cleaned as described in the ‘Ethics and dissemination - Benefits and risks assessment, group relatedness’ paragraph. Participants in the control group will receive usual care. Richard-Lalonde *et al*²⁴ found that music interventions of at least 20–30 min significantly reduced pain scores compared with 10–15 min in critically ill patients.²⁴ Furthermore, Chlan *et al* and Fu *et al*^{17 25} found that a total of 80–120 min per day music intervention leads to significant reduction in anxiety and sedative and analgesic medication requirement.^{16 17} Based on these studies, subjects allocated to the intervention arm will be offered to listen to music twice per day, in the morning and evening, with a duration of at least 30 min per session during 3 days after inclusion in addition to the standard care. Several studies suggest the importance of individual music preference of ICU patients in the effectiveness of the music intervention.^{20 24} Furthermore, since it is likely that loud and/or rock music may lack the right qualities for this setting, during the trial we will advise against listening to rock music and heavy metal.²⁶ The intervention will take place at moments when it is suitable for the caregivers (physicians, nurses and so on) and will not stand in the way of daily practice. The first session will take place in the morning, between 09:00 AM and 12:00 PM, the day after inclusion. In agreement with the direct caregivers, participants will be allowed to listen longer (per session or after the intervention period of 3 days) to music as requested by the patient or legal representative, in collaboration with the ICU nurse or researcher. Additionally, when patients listen to music apart from the music applied with the headphones within the trial protocol, this will be documented by a certified ICU nurse or research team members. The evening session will take place in the evening before intended sleep, for example, between 20:00 and 23:00 hours. Music intervention will be provided through over-the-ear headphones connected through Bluetooth to a tablet. The research team will provide a music device on an application with online prerecorded music lists, based on genre, artist and so on will be available. Participants or their legal representative will be able to choose their preferred music. Music intervention will be offered during 3 days after inclusion. Patients in the control group will receive the standard care procedure. See online supplemental file 1 for the template for intervention description and replication (TIDieR) checklist.²⁷

Study parameters

The main study parameter is VAS-A. Since routine assessment of anxiety is currently not part of the standard care and is based on clinical assessment, we choose for the VAS-A as a clinically easy applicable assessment tool. The VAS-A is a patient reported outcome and ranges from 0

to 10, whereas 0 is defined a ‘no feeling of anxiety’ and 10 as ‘most anxious ever’. The VAS-A is validated as a reliable self-rating tool for state anxiety and has been used in the intensive care setting.^{16 23 28}

The secondary study parameters are:

- ▶ Anxiety, assessed using the six-item short version of the State-Trait Anxiety Inventory (STAI-6).²⁹ The STAI-6 is added as an additional anxiety assessment since it can assess anxiety based on state anxiety, or anxiety about an event, and trait anxiety, or anxiety level as a personal characteristic. The full form of the STAI is a 40-item questionnaire and is considered invasive mainly because of the length, especially in study populations as the critically ill. Therefore, the STAI-6 is chosen for the current study. The STAI-6 has a high internal reliability and correlation with the full-form STAI, has been validated in Dutch and has been used in critically ill patients.^{23 29–32}
- ▶ Sleep quality, assessed by using a single-item questionnaire, as used in a recent multicentre randomised controlled trial studying haloperidol for ICU delirium (EuRIDICE).³³ This is a visual numeric scale ranging from one to seven, in which one indicates ‘did not/barely sleep’ and seven indicates ‘slept very well’.
- ▶ Pain, measured using the Critical-Care Pain observation (CPOT) in mechanically ventilated patients who are not able to communicate their level of pain, or the NRS/VAS for pain in non-ventilated and alert/oriented as part of the standard care by nurses.⁴
- ▶ Medication requirement (duration and dosages, corrected for body weight milligram/kilogram), including remifentanyl, propofol, benzodiazepines, dexmedetomidine, clonidine, paracetamol, sufentanil, fentanyl, morphine, ketamine, epidural analgesia, haloperidol and other benzodiazepines, atypical anxiolytics and antipsychotics.
- ▶ Agitation and sedation level, using the RASS, assessed three times daily during every shift by the nurse, as long as the patient is mechanically ventilated and/or sedated.² The RASS is a validated and reliable tool in the ICU.^{34 35} The score ranges from +4 (indicating highest level of agitation, eg, patient is aggressive) to –5 (indicating level of sedation, patient is not arousable). The goal is generally to achieve a RASS score of –2 to 0 which indicates that the patient is alert and calm.
- ▶ Delirium, as measured with the Intensive Care Delirium Screening Checklist (ICDSC), which is routinely done in all ICU patients, three times daily.^{4 36}
- ▶ Complications related to agitation, defined as removal of lines and tube (self-extubation) by the patient.
- ▶ Time spent on mechanical ventilation, measured in total amount of hours.
- ▶ ICU LOS, measured in total amount of hours spend in the ICU after inclusion.
- ▶ Physical parameters, daily heart rate (HR) and arterial blood pressure (MAP) at the time when the primary outcome (anxiety) is assessed during the intervention

period will be collected and analysed, in order to gain insight in proxy-measures for stress level.

- ▶ Patient memory and experience, assessed by the ICU memory tool (ICUMT)³⁷ extended with self-made questions to assess ICU experience. We adapted and shortened the ICUMT to a seven-item questionnaire to avoid overlap, for example, with assessment of anxiety or delirium, and with other tools and to avoid invasive long questionnaires. For the patient experience assessment in the music group, the questionnaire is extended with five items and for the control group with three items.

Other study parameters are:

Data on the following patient characteristics will be extracted from the electronic patient database:

- ▶ Age.
- ▶ Gender.
- ▶ Reason for and duration of hospital and ICU admission.
- ▶ Medical and surgical history.
- ▶ sedative, analgesic and anxiolytic/antipsychotic medication use 24 hours prior enrolment.
- ▶ Acute Physiology and Chronic Health Evaluation IV (APACHE-IV).³⁸

Study procedure

The planned start and completion dates of the study are set at, respectively, 1 July 2020 and 1 January 2022. Eligible patients or their legal representative admitted to the ICU will be informed and asked for participation. Participants in the music group will listen to music based on their preference. Participants in the control group will receive the standard care procedure. After inclusion and randomisation by a member of the research team, the importance of music in daily life and patients music preference using an eight-item questionnaire based on the tool assessed by Chlan *et al* will be assessed.²⁵ This tool is a 13-item questionnaire of which we collided item 7, 9, 10 and 11 and did not use items 12 and 13. Choice for music will be based on the preferred music list of the patient chosen from an online music application. If the patients' legal representative gave permission, the preferred music of the participant will be assessed by this person. After the intervention period when the patient is in better condition, the questionnaire will be assessed completely by the participant in order to further specify the music preference of the participant. In both groups, if patient is not able to initiate sleep, ear-buds will be offered to enhance sleep quality. [Figure 1](#) shows a flowchart of the study procedure. Start of the study period will be set at 00:00 hours the day after inclusion.

Music sound levels will be set at a level that is comfortable for the subject. If patients wear hearing aids, the hearing aid will be removed and then the sound level of the music will be set.

A member of the research team will assess anxiety, VAS-A and STAI-6, immediately after the music intervention in the morning and evening during 3 days after inclusion.

In the control group, anxiety will be assessed once in the morning (eg, after care provided by the nurses) and once in the evening before bedtime. If patients in the music group fall asleep during the evening music session, we will score the anxiety as 'zero', since music possibly reduced anxiety and thus promoted sleep. Sleep quality, of the night before, will be assessed daily in the morning after awakening, and before the music session in the music group, during 4 days.

The ICDSC and CAM-ICU are diagnostic nursing screening tools that can facilitate early recognition of delirium and are assessed three times per day by the nurse, once during each shift. The APACHE IV is assessed once at admission to the ICU. Total time music intervention used will be assessed by registration of the frequency and duration the patient listened to music in both groups, which will be assessed by the research team and not by the patient.

Collection of delirium scores, APACHE IV, medication use, self-extubation and ICU/hospital LOS, HR and MAP are part of the standard care; thus, a member of the research team will collect data on these parameters during the entire ICU stay from the patient's electronic medical file. The amount of medication administered will be extracted from the patients electronic medical file and calculated per hour based on the number of hours of a particular day (24 hours, unless first or last day of study).

In order to facilitate easy and adequate data collection a package per patient will be provided including the following questionnaires: anxiety, sleep quality, importance of music in daily life, ICU memory and experience and extra music intervention (assessed by the research team). After the intervention period, when participants are capable (alert, adequate and admitted to the nursing ward) of completing the questionnaires, they will be asked, before hospital discharge, to assess importance of music in daily life and the ICU memory and experience questionnaire will be asked to fill in at 2 weeks after discharge from the ICU.

Data on pain, delirium, medication requirement, physical parameters and complications related to agitation and RASS will be collected until 7 days after inclusion. Patients who withdraw from the study or otherwise cannot comply with the measures for the primary outcome will be replaced, to obtain the number of subjects for the sample size calculation.

Sample size

For the sample size calculation, we assumed a treatment effect based on the study of Chlan *et al*.¹⁶ They report a mean VAS-A of 50.5 mm with a SD of 29.2 mm in the ICU population. They found a reduction of 19.5 mm when music intervention is provided. To achieve a global significance level of 5%, a significance level of 1.7% based on the Bonferroni correction will be used for each of the three VAS-A tests (on day 1, 2 and 3 after inclusion), accounting for multiple testing and to obtain a power of 80%, planning two-sided testing, and a dropout rate of

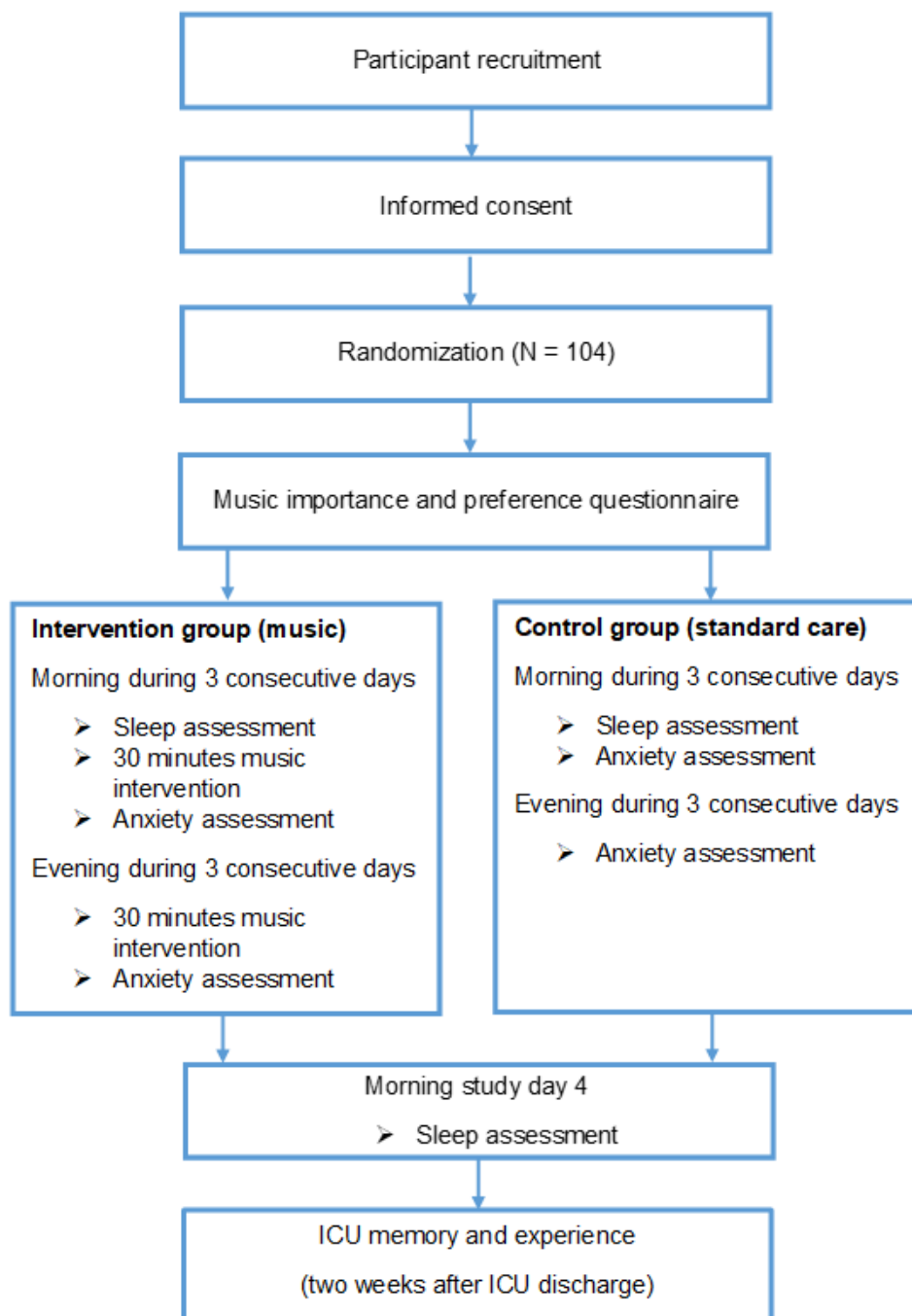


Figure 1 Flowchart study procedure. ICU, intensive care unit.

10%. Consequently, the sample size will be 104, which means 52 in each study arm. (This sample size calculation was performed using <https://clincalc.com/stats/sample-size.aspx>.)

Statistical analysis

Normally distributed continuous data will be analysed using the students t-test, using intention-to-treat (ITT) analysis, data will be presented as means with their standard deviation (\pm SD). Non-normally distributed continuous data will be analysed using the non-parametric Mann-Whitney U test, outcomes will be presented as median and IQR. Normality of continuous variables will

be assessed with the Shapiro-Wilk test and graphically in Q-Q plots. Homogeneity of variances will be tested using the Levene's test. Categorical data will be analysed using the χ^2 test or the Fisher's exact test (in case of <5 subjects per group). If a significant amount of data is missing, missing values will be replaced using multiple imputations. A two-sided $p < 0.05$ will be considered statistically significant.

Our primary outcome, the mean VAS-A, will be analysed using the students t-test as this measure is assumed to be continuous and normally distributed for day one to three separately. The total mean of the VAS-A will also

be analysed separately. Secondary to the ITT analysis, a per-protocol analysis will be performed. In case of statistically significant differences in baseline characteristics, we will estimate a linear regression with VAS-A as dependent variable, treatment group dummy as covariate controlled for the significant different baseline characteristics. The secondary outcomes are continuous and will be analysed using similar statistical strategy as the primary outcome. Differences between the categorical secondary outcome will be analysed using Fisher's exact test when no significant differences in baseline characteristics. When there are baseline characteristics statistically different between treatment groups, we will estimate binary logistic regression with similar setup as the primary linear regressions. Also, we will compare the VAS-A measures on day 0 and day 3 using a repeated measures analysis of variance to compare both groups over the two periods (or linear mixed models in case of missing data). The baseline characteristics will be summarised using median and 25th and 75th quartiles and number (percentage) for continuous and categorical variables, respectively. Interim analysis will not be performed for this study.

Data management

Data handling and storage will be performed according to the Dutch Personal Data Protection Regulation. Data will be stored in a database provided by the Erasmus MC. Data will be handled confidentially and anonymously, limited number of personnel will be permitted to access data. Data will be encoded with a unique study number that is related to individual participants of the study. A subject identification code list will be conducted in order to trace data to an individual participant. Only authorised personnel can view data that can be traced to individual persons, including members of the research team, the Medical Research Ethics Committee of the participating site and the healthcare inspection. Principal Investigator of the study will secure the code. Data will be stored in a protected location during the study and 15 years after end of the study.

Trial monitoring

Since there are no risks associated with the intervention in this randomised controlled trial and all participants will receive the standard medical care during the study, participants will have no larger risks than patients who are not participating in this study. Therefore, monitoring will not be applied in this trial.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics and dissemination

Ethics

The Medical Ethics Review Board of the Erasmus MC in Rotterdam has reviewed and approved the study protocol (MEC2020-0212). The first patient was included in

the Erasmus MC on 24 August 2020. This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act. The trial is registered in the Netherlands Trial Register (www.trialregister.nl, ID: NL8595) and the United States National Library of Medicine (www.clinicaltrials.gov, ID: NCT04796389). Two general hospitals (Haga Hospital, location Leyweg, The Hague and Ikazia Hospital, Rotterdam) in the Netherlands were added as participating centres after an amendment (protocol version: 2.0) which was approved on 07-12-2020. Eligible patients, meeting all the inclusion criteria and none of the exclusion criteria, will be informed about the study and asked to sign a written informed consent. Either the attending physician, the coordinating investigator or research assistant will provide information verbally. Eligible patients and/or their legal representative will receive an information folder and an informed consent form and will have a maximum of 48 hours to consider their participation. Participation in this study is on voluntary basis. If patients do not wish to participate, they can do so without providing a reason. Since the intervention is non-invasive and is not associated with any risks, the period for considering participation is justified. The general practitioner of the patient will not be informed about the participation to this study, considering the music intervention does not know any risks. Minors are not involved in this study. Participants will be excluded from the study when showing signs of resistance and thus will not undergo the intervention. At any moment during the study, patients are allowed to withdraw informed consent without being obligated for giving explanation. Since participants will have no larger risks, the Medical Research Ethics Committee Erasmus MC has given dispensation from statutory obligation to provide insurance for subjects participating in medical research (article 7, subsection 6 of the WMO and Medical Research (Human Subjects) Compulsory Insurance Decree of 23 June 2003). The reason for this dispensation is that participation in this study is without risks.

Benefits and risks assessment, group relatedness

Music as an intervention is unrelated to negative side effects or any other risks. As recommended by the WHO, the maximum sound level will be set at 85 dB in order to prevent hearing damage. The applied maximum sound level in this study is below the maximum noise exposure of 90 dB during 8 hours advised by the Occupational Safety and Health Administration of the United States Department of Labor. Considering the above, we can the risk of the music intervention is negligible. In advice of the Erasmus MC auditory centre, in patients using hearing aids, the volume lock will not be applied. The sound equipment (headphones and tablet) will be cleaned with a damp microfiber cloth, as advised by the Erasmus MC Infection Prevention Unit after a subject. If the patient has an indication for isolation, the sound

equipment should be first cleaned with a damp micro-fiber cloth and then disinfected with 70% alcohol or 100% chlorine. As an additional hygiene measure, disposable headphone covers will be used for each subject in the study. Participation to this study will not be compensated in any form. The reason patients may consent in participation to this study could be the already proven effects of the music intervention the patient may or may not experience. In addition, motivation for participation could be to improve care for future patients.

Dissemination

Research data can be presented or publicised in agreement with the principal investigator and project leaders only. Research data that can be traced to the individual will not be presented or published. The primary publication will be made by the principal investigator and research team. There are no competing interests between authors. The order of the different authors is not yet known. Final findings will be reported according to the CONSORT guidelines. The funder will have no role in the data collection process, data-analysis and interpretation of the trial results.

Ethics approval

The study protocol has received ethical approval from the Medical Ethical Review Committee of the Erasmus Medical Centre in Rotterdam prior to the beginning of the study.

Contributors Conceived and designed the study: EK, MvM, JJ and MvdJ. Refined the study design and obtained ethical approval: EK, MvM, JJ, DG and MJ. Wrote and revised this manuscript (fully or in part): EK, MvM, JJ, DG and MvdJ.

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